CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-229

MEDICAL REVIEW

DATE: May 31, 2003

FROM: Hugo E. Gallo-Torres, MD, PhD, PNS
Medical Team Leader
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

SUBJECT: NDA 21-229 (Prilosec OTC™; Omeprazole Magnesium Delayed Release Tablets for OTC use)
Sponsor: AstraZeneca
Sponsor's Agent: Proctor and Gamble Co.
Re: Recommendation for Approval

TO: Robert Justice, MD, MSc
Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180

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I. Background/Introduction

Omeprazole (OME) belongs to the proton pump inhibitor (PPI) class. OME is a substituted benzimidazole which irreversibly inhibits the H^+, K^+-ATPase enzyme system ("proton pump") located at the apical membrane of the parietal cell of the stomach.[1] It is worth noting, from the start, that although OME is a very good anti-secretory drug, it exhibits a **short PK half-life** (0.5 to 1h), and **slow onset** (acid inhibition of only 50% of maximum at 24h) but **long-acting PD effect.** In contrast to other anti-secretory drugs, such as antacids and H_2-receptor antagonists[2], which **provide rapid onset of action** because they start to inhibit gastric acid secretion within minutes after their administration, OME **prolonged inhibition** of gastric acid secretion **(to any stimuli) is delayed for a few hours,** stabilizes after 3 to 4 days and returns to baseline within 3 to 5 days after therapy discontinuation.

- The initial IND for OME was submitted 12/21/83 (indication: treatment of duodenal ulcer). On 07/18/84 the sponsor put the IND on clinical hold because a 2-year carcinogenicity study in rats showed **gastric carcinoids**. The **clinical hold was removed on 09/23/85** after agreement with the Agency that the carcinoid issue seemed related to profound and long-lasting acid inhibition, with the resulting **hypergastrinemia** playing a pivotal role in the observed **hyperplasia of the EC-L cell.**
- NDA 19-810 was approved on 09/14/87 for the (short-term) treatment of symptomatic gastro-esophageal reflux disease (s-GERD) at the dose of 20 mg once-a-day and treatment (healing) of erosive esophagitis (EE) also at the dose of **20 mg once-a-day**. By this time, Prilosec Delayed-Release capsules has been approved as prescription drug product for several indications in which effective treatment depends on inhibition of gastric acid secretion.[3] In addition to the aforementioned short-term treatment of s-GERD and EE, these indications include short-term (4 to 8 weeks) treatment of active duodenal ulcer, active gastric ulcer, maintenance of healing of erosive esophagitis (12 months) and treatment of pathological hypersecretory conditions.
- In an initial submission, dated January 27, 2000, the sponsor sought to market OTC OME for the same indication for which OTC antacids and OTC H_2-receptor antagonists (at a fraction of the prescription dose) are approved: **"relief of heartburn, acid indigestion and sour stomach and prevention of these symptoms brought on by consuming foods and beverages".** Review of the evidence demonstrated that OME, like all other PPIs, **is not suitable** for this indication.[4]

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[1] OME is a pro-drug and a lipid-soluble weak base that, at neutral pH, is devoid of gastric acid inhibitory effect. Following its systemic absorption, OME reaches the gastric parietal cell, becomes protonated (ionized) and rearranges to form a sulphenic acid and sulfenamide. The sulfenamide species reacts covalently with the sulphydryl group of the H^+, K^+-ATPase enzyme to inhibit gastric acid secretion.

[2] Cimetidine (Tagamet), ranitidine (Zantac), famotidine (Pepcid) and nizatidine (Axid).

[3] Other PPIs marketed for similar indications include lansoprazole (Prevacid), rabeprazole (Aciphex), pantoprazole (Protonix) and esomeprazole (Nexium).

[4] The evidence consisted of 4 studies: 2 (**092 and 095**) designed to assess heartburn relief acutely which showed no statistically significant difference between OME-Mg (10 or 20 mg once-a-day) and placebo and 2 (**005 and 006**) designed to evaluate the effect of 10 or 20 mg doses of OME-Mg in the prevention of **meal stimulated heartburn.** These last 2 studies showed inconsistent results.

- A Not Approvable letter, dated November 27, 2000 , was sent to the sponsor
- NDA 21-229, OME-MG Delayed-Release Tablets, was resubmitted on February 12, 2002 for the following proposed use: **"for prevention of frequent heartburn". Intended for those who suffer heartburn two or more days a week.** The Division's GI Team concluded that the population chosen by the sponsor **overlaps** significantly with those individuals that have symptoms that are consistent with the diagnosis of GERD, which could present either as s-GERD (heartburn et al. but no esophageal lesions) or EE (heartburn et al. with esophageal lesions). It was (and continues to be) our position that important clinical management/treatment issues pertaining to GERD patients to be treated with OTC OME **needed to be thoroughly addressed**. It was repeatedly noted that GERD is a **chronic relapsing condition that subsumes patients with mucosal erosions/ulcerations that require an adequate duration of treatment of inflammation.** In outpatient settings, a **4 to 6 week** initial course of adequate dosing with OME or other PPIs is prescribed.
- The appropriateness of OTC OME, with clear identification of **opportunities and constraints,** was discussed by the MTL in a memorandum dated October 23, 2000. Listed among the Discussion Points were: 1) determination of the adequate dose; 2) establishment of the duration of administration; 3) the **impracticability of treating GERD (whether symptomatic GERD or erosive esophagitis)** short-term; 4) lingering concerns about safety that needed to be properly addressed in the labeling; 5) use of drug in adolescent and younger children; 6) further discussion on OME and genotoxicity; 7) need for prospective or nested case control trials to characterize potential embryo-fatal damage in humans in view of the clastogenic properties of the drug; 8) masking and/or delaying the diagnosis of GERD complications and malignancy; 9) tumorigenic potential of drug-induced hypergastrinemia, and 10) exaggerated rebound of gastric acid secretion and recurrence of esophageal lesions upon drug discontinuation.

II. Summary Recommendations from Advisory Committee Meetings

- At the Non-Prescription Drug/Gastrointestinal Drugs (NPDGIDAC) Joint Advisory Committee of October 20, 2000, the sponsor's presentations included an overview on GERD by Dr. Donald O. Castell[5]. He noted that symptoms may not be a good measure of disease severity, since progression of disease is seen in asymptomatic patients. Moreover, **esophagitis may progress even with intensive therapy**. In addition, the greater the severity of esophagitis, the lower the healing rate, and **larger doses (of PPIs) are often required for higher grades of esophagitis**. Dr. Castell **stressed that GERD usually recurs after effective treatment.** He concluded that OME was suitable for an OTC indication, that the safety of long-term OME had been established; and that masking of important disease was unlikely if properly labeled. Dr. Castell concluded his presentation by noting that this approach

[5] The presentation by this **renown esophagologist** was entitled **"Proton Pump Inhibition in the Self-Management of Heartburn"**

(making OME available OTC) may bring more heartburn patients to physicians. In reply to the question **"Is the treatment of common heartburn as well as GERD an acceptable OTC indication?"** 7 members of the Committee voted **YES, 6** voted **NO** and 1 abstained.

- The February 12, 2002 resubmission for the newly proposed indication (prevention of the symptoms of frequent heartburn for 24 hours) was discussed at the joint meeting of the NPDGIDAC on June 21, 2002. **Approval of the drug for the proposed indication was recommended. Also recommended was a new labeling comprehension study**. The Joint Advisory Committee felt that the proposed *"Uses"* section of the labeling was not ideal. Self-selection by consumers for use of this drug product was not demonstrated **(the Joint Advisory Committee was 15-NO and 3-YES for demonstration of self-selection).** At an August 08, 2002 telecon between Agency and sponsor representatives, the sponsor was told that **a revised draft labeling must be tested in a new labeling comprehension study and it must have a high rate of correct understanding.** Other issues discussed at this telecon were prevention vs treatment and time to action.

III. EFFICACY: Summary/Conclusions

- There were two adequate and well-controlled randomized clinical trials, **Studies 171 and 183** that demonstrated that **OME is effective and well differentiated from placebo in the 24-h prevention of symptoms of heartburn for up to 14 days.**
- The Medical Officer reviewer proposed and the MTL agrees that this new indication represents **management of GERD.**
- **The study population consisted of patients with GERD**. Patients randomized into these trials had heartburn of greater than 1 month duration, with a frequency of at least 2 days per week. The patients were antacid or OTC H_2-receptor antagonist responsive (enriched population). In 80% of the patients the baseline heartburn frequency was $\geq$ 50% of days. The mean severity was 1.5 (2= moderate severity).
- The results (Table 1) showed:
  - **replicated statistically significant difference compared to placebo**
  - **efficacy at both the 10 mg and the 20 mg dose levels.** One Study (No. 171) showed superiority of the 20 mg over the 10 mg once-a-day level. This finding was not replicated in the other trial.
  - efficacy **increased over time.** On Day 1, the therapeutic gain (Table 1) varied between 9 to 17%. On Day 14, the therapeutic gain (data not shown in Table 1), the therapeutic gain varied between 23 to 30%.

Table 1
NDA 21-229
24-h Prevention of Heartburn Following the First Dose

	OME (mg/d)			Therapeutic gain/[p-value]		
Study 171						
	PL [n = 519]	**10 [n = 518]**	**20 [n = 523]**	**10 vs PL**	**20 vs PL**	**20 vs 10**
Responders	**169 (32.6%)**	**215 (41.5%)**	**260 (49.7%)**	**8.9% [0.003]**	**17.1% [<0.001]**	**8.2% [0.008]**
Study 183						
	[n = 520]	**[n = 520]**	**[n = 524]**			
Responders	**167 (32.1%)**	**235 (45.2%)**	**245 (46.8%)**	**13.1% [<0.001]**	**14.8% [<0.001]**	**1.6% [N.S]**
Definition of Responder (Primary Efficacy Endpoint): • **No heartburn over 24 hours on Day 1**						

Conclusions from the Daily Dose 24-Hour Prevention Studies:

1. Successful prevention of heartburn symptoms with 10 mg and 20 mg dose levels
2. Increased efficacy over time
3. Benefit lost within 3 days of discontinuation of test medication (not shown in Table 1)
4. Only Study 171 showed superiority of OME-Mg to placebo in the 2-week prevention of **nocturnal heartburn.**

IV. SAFETY : Summary/Conclusions

Many aspects of the safety profile of prescription OME and the suitability of the drug for OTC use are discussed in Dr. M. Avigan's review of NDA 21-229[6] and his, as well as the sponsor's, presentation at the October 20, 2000 Joint Advisory Committee meeting. Materials from these documents and discussions at the Joint Advisory Committee meeting are highlighted below.

- OME was introduced in Europe in 1988 and in the U.S. in 1989. The indications for use have included the various acid-related GI disorders mentioned in Section I of the current review, and other off-label conditions.
- Since its introduction, ca. 300 million courses of OME patient treatments have been prescribed world-wide in 103 countries, with 90 million courses in the U.S.
- OME-Mg is approved for prescription use in 26 countries[7]; it is available under the trade names of LOSEC, LOSEC tablets, and LOSEC MUPS, since February of 1998.

SOURCES

The safety information for the proposed OTC indication is derived from 3 sources: **1.)** OTC clinical trials [n = 8,179] where subjects were administered 10 or 20 mg daily doses of the drug for 1 to 14 days; **2.)** prescription clinical trials [n = 5,757] where patients were administered 10 to 40 mg daily doses of the drug for 1 day to 12 weeks; and **3.)** two Post-Marketing Surveillance Databases: SafeTNet [n = 15,385] until 06/30/98 and OME-Mg [02/98 to 12/99].

- The following incidences were noted in the safety experience from OTC trials:

Headache	**5%**
Infection	**2%**
Diarrhea	**2%**
Serum Sickness	**1 case**
Urticaria	**4 cases**
Elevation of AST	**7 cases**

There were no dose-related differences.
The drug was withdrawn in 13 patients **[headache, n = 10; rash, n = 3]**
Two deaths were reported, neither related to the drug.

Conclusion: the AE profile of OME-Mg, under the experimental OTC conditions is **similar to the (mostly short-term) prescription experience.**

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[6] For the review of the OTC OME NDA, a **modular approach was used**. Dr. L. Goldkind reviewed Efficacy (Section III of the current review). Most aspects of Safety were reviewed by Dr. M. Avigan while Dr. S. Kress reviewed Specialized Aspects of Safety.

[7] OME-Mg is available in Canada as a prescription delayed-released (enteric-coated) tablet, which is a different formulation than the MUPS formulation. OME-Mg **is approved for OTC use only in Sweden, available as LOSEC MUPS** since early 2000. OME-Mg MUPS has never been marketed in the U.S. and is the proposed formulation for OTC marketing.

Liver Injury
No dose-related toxicity was reported in a total of 9 trials [n = 1,409], where patients **(primarily GERD-related indications)** were administered OME for between 1 to 60 weeks. Between 2/1000 and 5/1000 treated patients developed LFT abnormalities (elevations of transaminases $\geq$ 3 x normal). **Most abnormalities were mild and transient**[8].

Conclusion: When all information on liver injury is considered, the conclusion is reached that OME **is a hepatotoxin.** However, the number of very serious AEs is rather small in the prescription arena. Nonetheless, the switch from prescription to OTC should consider the possibility of drug-drug interactions with other OTC available hepatotoxins (i.e. acetaminophen), in an uncontrolled environment.

Skin Toxicity
The SafeTNet database includes 49 cases of toxic epidermal necrolysis and Stevens-Johnson syndrome, 2 assigned an "A" rating (1 fatal, 1 non-fatal). These cases are characterized by a variable time between exposure and onset of symptoms.

Agranulocytosis/Bone Marrow Suppression
- In U.S. trials, the incidence of white blood cell suppression has been: granulocytopenia, 0.2 % to 0.7 %; leukopenia, 0.9% to 1.5 %.
- Incidences from the Intensive Medical Monitoring Program (New Zealand) are: granulocytopenia, 0.03 %; aplastic anemia, 0.01 %
- WBC suppression SafeTNet experience includes : a) 26 fatalities, 5 of which were assigned an "A" rating and b) 96 serious non-fatal cases, 35 of which were assigned an "A" rating.

Immediate hypersensitivity reactions
- These have included angioedema/anaphylaxis, urticaria (1 to 2 per 1000) and wheezing.
- The incidence of angioedema/urticaria in New Zealand Monitoring database is 0.46 per 1000.
- Serious hypersensitivity AEs from the SafetNet included 134 cases of angioedema/anaphylaxis.

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[8] The post-marketing liver toxicity data from SafeTNet include : a)33 fatal cases, two in which there was no other explanation of causality ("A" rating); and b) 227 non-fatal serious cases, 4 of which were assigned "A" rating (2 positive rechallenges). The FDA Adverse Event Reporting System (AERS) includes 2 liver transplants.

It is also important to note that the currently approved labeling for Prilosec includes the following information in the ADVERSE REACTIONS section:

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

Conclusion: there is some concern about the occurrence of hypersensitivity reactions with prescription OME (1/2000). This may contribute to the reluctance to switching from the prescription to the OTC arena.

However, after appraising the information from the Swedish Post –Marketing 1988-1999 voluntary reporting, Dr. Avigan concluded (and the MTL agrees with this conclusion) that serious non-fatal AEs included reports of reactions that were qualitatively similar to the U.S. experience: hypersensitivity reactions, liver toxicity, toxic epidermal necrolysis interstitial nephritis and bone marrow suppression.

Therefore, the overall conclusion is that there is not apparent differences between safety profiles of enteric-coated prescription formulation and magnesium formulation.

SPECIAL AREAS OF INTEREST

1. Drug-Drug Interactions

- It is well established that OME interacts with the following cytochrome P_{450} enzymes : CYP2C19 (lack of which in "slow metabolizers" is an important consideration), CYP3A4 (a minor pathway for OME), CYP1A2, CYP2CP, CYP2D6 and CYP2E1.
- **The general consensus is that although many interactions can be demonstrated, only a few (properly addressed in the Prilosec labeling) are of clinical relevance.**
- Included are those that may involve CYP2C19 "slow metabolizers" (3 % Caucasians, 15 % Asians), and where aging and liver disease may play an important role. "SMs" or people with underlying medical conditions may have pronounced changes of CYP2C19.

2. Special Populations

- Safety in **adolescents** has not been established because: a) age-related responses have not been assessed; and b) age-related toxicities cannot be ruled out.
  NOTE: This concern due to lack of information is reflected in the Draft labeling.

- There is some controversy with regard to OME and **genotoxicity,** a subject matter that was amply discussed at the October 20, 2000 AC meeting, with no clear resolution.

- Regarding use in **Pregnancy**, OME is categorized as a "Class C" drug because of embryo-fetal and postnatal toxicity in animal models[9]. The drug has clastogenic properties.

- Although substantial human use has not revealed a "signal", there is need for prospective or nested case control studies to properly characterize potential embryo-fetal damage in humans.
  NOTE: These concerns are not unique to the proposed OTC use of OME. They are also applicable to the prescription arena.

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[9] Included among these are rabbit embryo-fetal lethality, reduced rat fetal weights, reduced survival/growth and slowed behavioral development in rat offspring.

3. Safety Issues Related to Long-Term Use

These include: a) masking and/or delaying in the complications of GERD and malignancy; b) tumorigenic potential of drug-induced **hypergastrinemia** and the above-mentioned genotoxicity; c) exaggerated rebound of gastric acid secretion/recurrence of esophageal lesions upon drug discontinuation; and d) issues specifically related to long-term OTC use of OME in GERD.

a) There have been 49 gastric malignancy cases in SafeTNet (4/49 delay in diagnosis). The delay in diagnosis may be caused by temporary alleviation of symptoms and improvement in the appearance of endoscopically evaluated lesions.
- GERD complications of important public health consideration include: Barrett's esophagus[10] (up to 10 % of GERD patients, according to Dr. Castell's presentation to the October 20, 2000 Joint AC), in which the symptoms are not distinguishable from GERD

and

advanced stages of erosive esophagitis (2.4 to 47 %), in which the medical management is aggressive suppression of gastric acid secretion.

b) There is no question that OME (like other PPIs) induces **hypergastrinemia** but the question of whether hypergastrinemia is dangerous to man is a matter of debate, also applicable to the prescription arena.[11]

Studies aimed at determining a potential role for gastrin in carcinogenesis in the GI tract have yielded conflicting results. It is worth noting that gastrin is not mutagenic, but rather is mitogenic.

In summary, there seem to be important unanswered questions regarding the potential untoward effects of increased serum gastrin concentrations as a consequence of PPI (not just OME) administration. But again, these unsettled issues also apply to the use of the drug in the prescription arena.

There is no definite answer to the question of whether OME is tumorigenic in humans. Besides the above-mentioned genotoxicity and the trophic effects of hypergastrinemia, there is potential for exaggerated growth promoting effects in H. pylori infected individuals, a subject discussed at two GI Advisory Committee meetings. But the evidence for carcinogenicity in humans is rather weak because EC-L cell hyperplasia in humans, unlike rats, **is not linked to carcinoid tumors**, there is

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[10] Barrett's esophagus with dysplasia occurs in <1 % of patients. Delay in diagnosis would prevent surveillance. Esophageal adenocarcinoma occurs in < 1 % of patients. Delay in diagnosis would reduce the chances of survival.

[11] With OME administration, 2 to 4-fold increases in serum gastrin concentration are common. **These elevated concentrations reverse upon drug discontinuation.** These increases are not observed with "low dose" H_2-receptor antagonists. Pronounced hypergastrinemia occurs in "outliers". **Serum gastrin increase may be pronounced when the following conditions are present: H. pylori infection; CYP2C19 polymorphism (SM/EM or SM/SM); high dose and increased frequency of treatment; and low pre-treatment gastric acid secretion state.**

no apparent causal relationship with carcinoid tumors and other GI malignancies, and contribution in H. pylori infected subjects to the development of gastric mucosal atrophy, intestinal metaplasia, and dysplasia, is not apparent.

c) There is no question that rebound of gastric acid secretion occurs upon discontinuation of PPI and the this "biological response" is related to the administered dose.[12]
The following has been demonstrated with OME: cessation of treatment is associated with rapid reappearance of erosive esophagitis; acid rebound is reflected by increases in both basal- and pentagastrin-stimulated acid secretion; and acid rebound is self-limiting. But whether acid rebound plays a role to prolong (OTC) usage has not been studied **(although it is plausible)**; some investigators believe that H. pylori infection may influence the development of acid rebound. Pronounced acid rebound may not be detected in small studies.

d) **Issues related to long-term use of OME in GERD**
As previously noted, the PD effects of OME are long-lasting. With this PPI, maximal acid suppression occurs after 2 to 3 days of daily 20 mg doses. Based on numerous publications and due to the above-mentioned rebound of acid secretion, relapse of heartburn symptoms and/or esophageal inflammatory changes is predicted in some patients with GERD **who discontinue treatment after the initial 14-day course**. It is therefore possible that some patients may take a second and even a third course immediately after finishing the first. However, even in this instance, there are no overt safety concerns so that approval of the drug for OTC use can still be recommended is spite of these real possibilities.

OVERALL CONCLUSION ON SAFETY
Even though there are some controversial issues and answers to some safety questions are yet to be provided, the safety experience with prescription OME **is generally reassuring**.

From the evidence at hand, reviewed in some detail in the current document, and amply discussed at multidisciplinary levels and by several individuals or Committees, it is also concluded that **the safety profile of OME-Mg is suitable for OTC use.**

V. ACTUAL USE Studies

- Actual use studies in the initial NDA submission were reviewed by Drs. Ling Chin and Daiva Shetty[13] who found that the provided information was inadequate. Information on these actual use studies was also discussed at the

[12] One of the most convincing demonstrations of lesion/symptoms recurrence upon discontinuation of OME in GERD patients being treated with this drug long-term was reported by E. C. Klinkenberg-Knol et al [Scand J Gastroenterol 25:1144-1150 (1990)]. These authors studied the effect of sudden withdrawal of long-term maintenance therapy with OME for up to 4 years. These patients showed prompt normalization of serum gastrin concentration, and increased basal acid output. As a consequence, there was a fast recurrence and aggravation of GERD symptoms and endoscopically-proven signs of mucosal inflammation (erosive esophagitis).
[13] Reviewed studies have included : No. 003, 067, 014, 022, 091 and 1998003.

October 20, 2000 Joint Advisory Committee meeting. In the November 27, 2000 Not Aproval letter, the Agency informed the sponsor that the actual use study (as well as the label comprehension trial) had failed to demonstrate that consumers understood how and when to use Prilosec 1 in comparison to currently available OTC heartburn products that are marketed for relief and/or prevention of heartburn. The sponsor was advised that, in performing additional actual use studies, it will be important to demonstrate that consumers understand that this product **will not immediately relieve symptoms.**

- Dr. Shetty's review, dated May 9, 2002, included an assessment of the results of the Actual Use Trial #007 , A Multi-Center, Open-Label, Actual-Use study to Investigate How OTC Consumers Use Omeprazole Magnesium, 20.6 mg in "naturalistic" OTC conditions following proposed labeling instructions. The treated population (subjects who purchased and used the drug) consisted of 758 subjects. The enrolled population was reasonably balanced in terms of age and ethnicity, and representative of the general U.S. population. There were 60 % female and 40 % male, ranging in age from 18 to 91 years (mean = 48y); 65% of the subjects were Caucasian, 18% Black, 11% Hispanic and 6% made up other races. Overall , the correct self-selection was 83% for the primary population and compliance with the three labeled indications (take 1 tablet a day, every day for 14 days) was achieved by 63% of the treated population; 3 % of the subjects exceeded 14 consecutive days of treatment and 33 % took the medication for less than 14 days. **The study results showed that the majority of the consumers who self-selected and used the product, suffered from long-standing and frequent heartburn (GERD); 98 % of the subjects who used the drug had heartburn symptoms for more than 3 months (again, this is GERD).** Not surprisingly, the responses to the follow-up questionnaire (3 months after the study) showed that more than half (58 %) of the subjects available for follow-up had their heartburn return . Only 20% of the latter contacted their health care provider.

VI. LABEL COMPREHENSION Studies

- Results from an initial label comprehension study and an addendum, reviewed by Karen Lechter, JD, PhD, suggested potential for substantial use by persons who should consult a physician first. Dr. Lechter commented that some information could benefit from strengthening, and noted that the sponsor had not tested the most recent label, which differed considerably from the tested label.

- In a more recent review, dated May 2, 2003, Dr. Lechter evaluated results of the Study entitled "A Multi-Center Label Comprehension Study to Evaluate Consumer Comprehension of OTC Labeling Options for Omeprazole Magnesium Tablets". This study tested three different labels (A, B, and C) for OTC Prilosec. Participants were divided into Frequent and Infrequent heartburn sufferers, as well as low and high literacy groups. Dr. Lechter's main conclusions were:

1. **More scores were very high, regardless of the label.**[14]
2. The scores with label B were numerically higher than the other two, but a conclusion that label B was best overall was not overwhelmingly clear-cut .
3. Frequency of participants' heartburn had little effect on responses except among the low literate infrequent sufferers.[15]
4. In general, the low literate had more difficulty with some concepts than did the literate, with the largest difference in understanding occurring in the time of day for dosing, how often to repeat the treatment, and the time to full effect.
5. There was no indication that literacy level substantially affected understanding of warnings that appeared on the label.

6. There was ***good understanding*** for important components of the labels tested. These components include: almost all warnings, do not chew or crush, stop use and contact a doctor after 14 days of treatment if heartburn persists, contact a doctor if symptoms return in two months, it is acceptable to use the product again after six months and appropriate dose. For other components there was either moderate to lower understanding or indeterminate understanding. Dr. Lechter noted that for some questions, due to methodological issues, scores may have been inflated. These included questions on duration of use and action to be taken if heartburn continues after 14 days.

VII. UNRESOLVED ISSUES

- In a memorandum dated May 3, 2002 [16] which was the Division's contribution tro the Background Package for the June 21, 2002 Joint Advisory Committee meeting, the MTL listed six "unresolved issues". These included differentiation of OME-Mg from antacids and H_2-receptor antagonists, the adequate OTC dose, the adequate duration of treatment (28 vs 14 days), chronic or maintenance self-treatment, total number of courses per year, clarification of the appropriate and safe use of the drug in adolescents and younger children, and whether the availability of OME-Mg in an OTC setting would delay or prevent consumers from appropriate contact with their physicians. The MTL feels that, except as noted below, all of these concerns/issues have been resolved as a result of the close multidisciplinary interaction among Agency representatives and between FDA and sponsor representatives.
- Due to reasons discussed in detail in Section I. Background/Introduction of the current review, the MTL (and this is also the opinion of the reviewer gastroenterologists of NDA 21-229), reiterates his stance that the initial course of treatment of frequent heartburn in the OTC arena should be 28 rather than 14 days. However, it is hoped that the approach of self-medicating their condition for 14 rather than 28 days result in more consumers going to visit a health care provider earlier than otherwise.

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[14] Scores may have been inflated due to methodological inadequacies, so comprehension in actual use may be lower than represented by these results.

[15] Self-selection questions for the group of infrequent heartburn sufferers with low literacy were 10 to 18 points lower than for the literate individuals with infrequent heartburn.

[16] To Acting Director, HFD-180, Director, HFD-560 and Deputy Director, HFD-560

VIII. PACKAGE INSERT/DRUG FACTS

The latest version of these two documents, at this time in the final stages of internal circulation, contains modifications from many disciplines as well as agreements with the sponsor. These documents are ready for finalization.

In a telecon with Dr. Charles Ganley *(Director, HFD-560), the sponsor proposed the following changes The MTL suggestions are given in italics.

1.

2.

3.

IX. Medical Team Leader's Recommendations for Regulatory Action

NDA 21-229, for Prilosec OTC for the treatment of frequent heartburn should be approved.

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/s/

Hugo Gallo Torres
6/10/03 11:13:07 AM
MEDICAL OFFICER

Robert Justice
6/13/03 10:24:05 AM
MEDICAL OFFICER

OTC MEDICAL OFFICER'S REVIEW

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

NDA #:	**21-229**
Drug name:	**Prilosec OTC (omeprazole magnesium)**
Sponsor:	**AstraZeneca LP/Procter and Gamble Company**
Pharmacologic Category:	**Proton Pump Inhibitor**
Proposed Indications:	**For Prevention of Frequent Heartburn**
Dosage Form:	**20 mg Tablet**
Route of Administration:	**Oral**
Submission dates:	**December 20, 2002**
Review date:	**April 23, 2003**
Reviewer:	**Daiva Shetty, MD**

Table of Contents:

Executive Summary:

I. Recommendations

A. Recommendation on Approvability

The sponsor fulfilled the Agency's request for information for the Prilosec OTC Rx-to-OTC switch.

Since Label B is well understood, Prilosec OTC (omeprazole magnesium) 20 mg tablet should be approvable as an OTC product for the treatment of frequent heartburn with the following modifications of the label and package insert:

1. The "Uses" section of the label in addition to already listed 3 bullets, should include the following statements:

- [redacted]
- not intended for immediate relief of heartburn

2. In the section "Ask a doctor before use if you have", on the label as well as on the package insert: eliminate the words [redacted] The first and second bullets should be combined into one and rewritten as follows:

- had frequent heartburn over 3 months. This may be a sign of a more serious condition.

3. The section [redacted] on the package insert should have the fourth bullet:

- [redacted]

4. On the package insert, in the section '[redacted], the last sentence should be rewritten to: '[redacted]

B. Recommendation on Phase 4 Studies and Risk Management Steps

No specific new post-marketing studies are needed. The safety data submitted in this application did not present any safety signals that would preclude Prilosec from OTC marketing. Since a large uncontrolled population will be exposed to the drug after its Rx-to-OTC switch, post-approval safety should be vigilantly monitored, and submitted to the Agency as described in 21 CFR 314.50(d)(5)(vi)(b).

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

This is the second resubmission of the NDA for prescription to over-the-counter (Rx-to-OTC) switch of omeprazole magnesium tablet.

Omeprazole is a proton-pump inhibitor (PPI) approved for prescription use in 1989. The original NDA requesting to switch Prilosec (omeprazole magnesium, Ome-Mg) from

prescription to OTC status was submitted on January 27, 2000. The data were presented at the joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee on October 20, 2000. The original NDA was found to be non-approvable because of inadequate efficacy data to support the proposed treatment regimen, and inadequate data to demonstrate consumer ability to use Prilosec safely in the OTC setting.

On February 12, 2002 the sponsor resubmitted the NDA. In their resubmission the sponsor provided data to address deficiencies listed in the non-approvable letter. To discuss the new proposed target population, dose, and dosing directions, on June 21, 2002, the Agency held a second joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee. The majority of the members of the joint committee agreed with the sponsor's proposed target OTC population and the dosing directions. However, a majority of the members of the joint committee also felt that the sponsor should develop a better OTC label and test that label in the OTC setting prior to approval of omeprazole magnesium for OTC marketing. On August 8, 2002 the Agency issued an Approvable Letter and requested the sponsor to revise the labeling to include several concepts and to conduct a new label comprehension study.

The current submission is the sponsor's response to the Agency's Action Letter dated August 8, 2002. It contains results of one Label Comprehension Study (#22103), proposed OTC labeling, and the safety update.

B. Efficacy

No new efficacy data was presented in this NDA resubmission. The proposed target population and directions for use were addressed in the previous submission of February 12, 2002, and discussed at length at the June 21, 2002 joint Advisory Committee Meeting.

C. Safety

The integrated review of safety of omeprazole for the Rx-to-OTC switch was reviewed at the time of the original OTC NDA submission on January 27, 2000, and the February 12, 2002 Resubmission. Safety data submitted to the current application consisted of an international post-marketing experience with the Ome-Mg tablet from July 1, 2001 through September 30, 2002.

For the reporting period of July 1, 2001 through September 30, 2001, there were a total of 40 serious adverse event (38 non-fatal and 2 fatal) cases for Ome-Mg multiple unit pellet system (MUPS) tablets reported. The two reported fatal adverse events seem to be not directly related to omeprazole. One event was an intentional overdose. In addition, there were confounding factors in both of the cases.

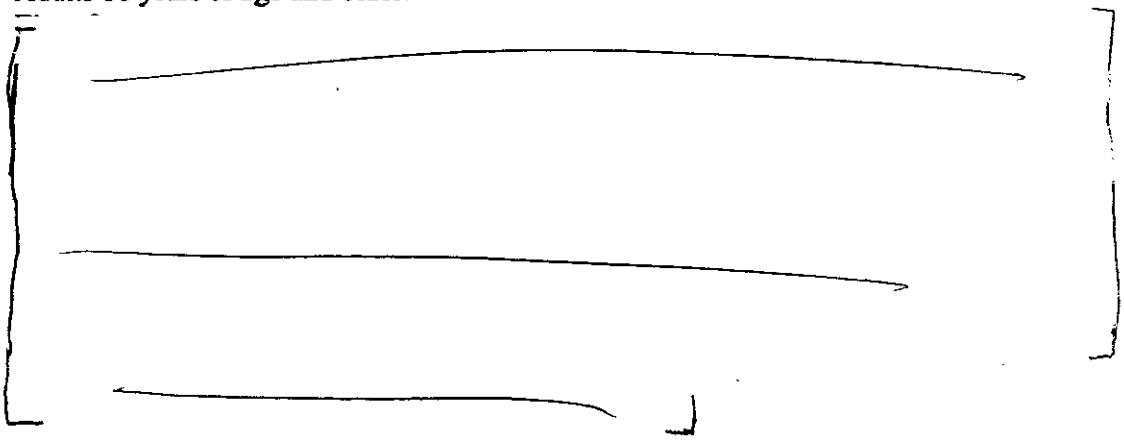
The reported serious adverse events are consistent with the previously reported safety profile of omeprazole magnesium tablets with one exception. Visual disturbances or eye

related adverse events are not listed in the Prilosec capsule prescription label. There are 8 eye-related adverse events occurring in 5 patients reported in the current safety update. Individual case reports have been reviewed. Two events, mydriasis and optic ischemic neuropathy occurring in two different patients, could possibly be attributable to the use of omeprazole. The other 3 patients had many confounding factors and, therefore, the causal relationship of adverse events to omeprazole cannot be assessed. A few non-serious adverse event reports related to visual disturbances were noted in the past safety data submissions. They seem to be rare occurrences considering the wide extent of use of the drug.

The safety of Prilosec has been well established by clinical trials supporting its approval as a prescription product. The safety data presented in this NDA resubmission show that no new serious signals attributable to either labeled use or misuse of the prescription product have appeared in the course of post-marketing surveillance. Thus, there is no new data to suggest that Prilosec would be unsafe for OTC marketing.

D. Dosing

The dosing regimen is acceptable as proposed:
Adults 18 years of age and older:



The proposed Prilosec OTC labeling is based on the recommendations of the Agency, the joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee, and the results of the Label Comprehension Study #22103. A summary of data from the Label Comprehension Study is presented below.

This was a multi-center, label comprehension study to evaluate how well consumers with heartburn understand the conditions (i.e., uses, warnings and directions) under which Prilosec OTC can be used based on their reading the carton label. Three different package labels were tested in four cohorts of consumers based on literacy (literate and low literate) and heartburn frequency (frequent and infrequent heartburn sufferers). Subjects were recruited in forty geographically dispersed shopping malls. Twelve additional sites (7 additional cities) were targeted to recruit low literate adults. A total of 1842 subjects participated in the study, approximately 450 consumers per cohort, with

150 assessing each of the three labels. There were 46% male and 54% female, with 56% Caucasian, 32% African American, 7% Hispanic and 5% representing other races. Almost half of the respondents (46%) were between the ages of 18 and 34 years; 39% were 35-54 years and 15% were 55 years or older. The distribution of gender, age and race within each of the labels were similar to the overall distribution.

Overall, there was a good understanding of the use of the product. Between 91.2% and 99.8% of the subjects understood correctly that the product was for treatment of frequent heartburn. There was no significant difference in comprehension of the "Uses" of the product between frequent and infrequent, and between literate and low literate heartburn sufferers. Data show that consumers understand well that Prilosec OTC is appropriate for the treatment of frequent heartburn. The comprehension that Prilosec is not intended for the treatment and/or prevention of infrequent/episodic heartburn was not as good, ranging from 84% to 92%. Comprehension scores in low literacy cohorts were lower, ranging from 74% to 88%.

There was good self-selection among frequent heartburn sufferers. Between 98% to 100% of subjects, irrespective to their literacy level, self-selected correctly. There was a statistically significant difference ($p < 0.001$) in self-selection between frequent and infrequent heartburn sufferers, with frequent heartburn sufferers self-selecting better. The most self-selection errors were among the low literate infrequent heartburn sufferers (70% to 77%). Even though there was no statistical significance between the three tested labels, low literate infrequent heartburn sufferers seemed to understand label B better than label A or C.

The warning section was identical in three labels tested. This is reflected in the comprehension results. Comprehension scores ranged from 93% to 99% among literate and from 71% to 99% among low literate subjects for the different elements of the warnings that were tested. There was no significant difference in comprehension of warnings within any subgroups for the three labels.

The study results demonstrate that there was a good understanding of directions for use of Prilosec OTC. The "Directions" sections on labels A and B were identical. Therefore, there is no surprise that these two labels did not differ in their comprehension scores. Label C had a different format and was least understood. Comprehension rates in this area for labels A and B ranged from 94% to 99% for literate and from 81% to 97% for low literate subjects. The concept of repeated courses of treatment, which was not included in the previous labels, was well understood. Between 90% and 99% of subjects correctly answered questions about the frequency and the timing of repeated 14-day courses of Prilosec OTC.

The concept about the expectations of efficacy for Prilosec OTC was included on label C only. It was well understood by literate (94.6%) and low literate subjects (87.9%). This concept is not included in the proposed package label. The sponsor's argument for not including the statement is that it did not help to increase comprehension related to episodic heartburn scenarios. In the opinion of this reviewer, the concept about the

expectations of full effect should be included on the drug label. Prilosec has a different mechanism of action than the other currently available OTC heartburn medicine and, therefore, information about the expected effect is warranted.

E. Special Populations

Prilosec OTC is a pregnancy category C drug. Issues with regard to the use of omeprazole magnesium by pregnant women have been addressed by HFD-180. The product label carries an appropriate pregnancy warning as specified in 21 CFR 201.63.

The drug is not labeled for children or adolescents less than 18 years of age. Omeprazole use in pediatric population will remain under the prescription label. The label has an adequate warning to consult a physician for use of Prilosec OTC under 18 years of age.

Clinical Review:

I. Introduction and Background

The sponsor is proposing to market omeprazole magnesium, 20 mg tablets under the trade name Prilosec OTC for consumers 18 years of age and older suffering from a frequent heartburn (2 or more days a week).

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

Adults 18 years of age and older:

[redacted]

There are two classes of drugs available OTC for heartburn relief: antacids and histamine-2 receptor antagonists (H_2RA, acid reducers). They are indicated for relief of heartburn symptoms. In addition, H_2RAs are approved for prevention of heartburn symptoms induced by meal. The list of currently available OTC drug products for the relief and/or prevention of heartburn symptoms is presented in Table 1 below.

Table 1. List of Currently Available OTC Products for Relief or Prevention of Heartburn Symptoms

Proprietary (pharmacological) Name	NDA/ANDA Number*	Pharmacological Category
Zantac 75 (ranitidine HCl)	20-520	H_2RA
Tagamet HB (cimetidine)	20-951	H_2RA
Pepcid AC (famotidine)	20-325	H_2RA
Axid AR (nizatidine)	20-555	H_2RA
Pepcid Complete (calcium carbonate, famotidine, magnesium hydroxide)	20-958	Combination Product
Gaviscon (aluminum hydroxide, magnesium trisilate)	18-685	Antacid Combination
Various trade names (Calcium carbonate; Aluminum hydroxide; Magnesium salts; Sodium bicarbonate, in combination or as single ingredients)	Final Monograph for Antacid Products for OTC Human Use	Antacids

* Only reference listed drugs are listed in the table. There are multiple generic drugs available, as well.

Omeprazole is a proton-pump inhibitor first approved in Europe in 1988, and in the United States in 1989. It is currently marketed in the U.S. as a capsule formulation for the following indications:

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

The omeprazole magnesium MUPS tablet formulation, first launched in Europe (Sweden) in February 1998, is currently available by prescription worldwide in 33 countries. To date, the MUPS tablet is available as an OTC product in Sweden only.

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

- The efficacy, appropriate dose and duration of therapy and use of Prilosec in the OTC setting were not adequately established. The ability of the consumer to appropriately

self-select and to use Prilosec safely and effectively in the OTC setting had not been demonstrated.

- The data had not adequately demonstrated the ability of consumers to comprehend the risks associated with specific drug interactions, nor the ability of consumers to avoid concomitant use of specific interacting drugs without the intervention of a physician.
- The sponsor did not provide adequate safety information to support OTC omeprazole use [redacted]
- The sponsor also had not established that consumers would not use Prilosec for extended periods of time without contacting a health care provider.

On February 12, 2002 the sponsor resubmitted the NDA. In their resubmission the sponsor provided data to address deficiencies listed in the non-approvable letter. The differences between the original submission and the first resubmission are listed in Table 2 below.

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

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

To discuss the new proposed target population, dose, and dosing directions, on June 21, 2002, the Agency held a second joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee. A majority of the members of the joint committee agreed with the sponsor's proposed target OTC population and the dosing directions. However, a majority of the members of the joint committee also felt

that the sponsor should develop a better OTC label and test the label in the OTC setting prior to the approval of omeprazole magnesium for OTC marketing. On August 8, 2002 the Agency issued an Approvable Letter and requested the sponsor to revise the labeling to include several concepts and to conduct a new label comprehension study. Concepts the Agency asked be included in the labeling and tested in a label comprehension study are listed below:

1. Determine if consumers understand that omeprazole magnesium tablets are not intended for the immediate treatment of heartburn, or the prevention of episodic (meal-induced) heartburn.
2. Determine if consumers with heartburn understand that omeprazole magnesium tablets may take 1 to 2 days of use to work.
3. Determine if consumers with heartburn understand when to see their doctor before and after starting treatment.
4. Determine if consumers understand when to ask a doctor before use if they have any of the label warning symptoms.
5. Determine if consumers understand the label use directions.

The current submission is the sponsor's response to the Agency's Action Letter dated August 8, 2002. It contains results of one Label Comprehension Study (#22103), proposed OTC labeling, and the safety update.

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

Refer to the original NDA for omeprazole Rx-to-OTC switch reviews. There is no new nonclinical information contained in this supplemental New Drug Application.

III. Human Pharmacokinetics and Pharmacodynamics

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

IV. Description of Clinical Data and Sources

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

1. Results of one label comprehension study,
2. Safety update, and
3. Proposed OTC labeling for 20 mg omeprazole magnesium tablet.

V. Clinical Review Methods

This review will cover the safety update, results of the Label Comprehension Study #22103, and related to it materials, and the proposed labeling. In addition, the Division of Surveillance, Research, and Communication Support (HFD-410) will review the label comprehension study.

Adverse event reports submitted by the sponsor were gathered from the sponsor's postmarketing surveillance system for Prilosec 20 mg tablets for the time period July 1, 2001 through September 30, 2002.

The label comprehension study was conducted as a follow-up to previously conducted label comprehension studies on omeprazole magnesium tablets, the Food and Drug Administration's (FDA's) feedback in the August 8, 2002 Action Letter, and the October 9, 2002 End-of-Review meeting. There were no DSI audits conducted for the study site or data analyses. The sponsor did not provide a financial disclosure as this study does not meet a definition of clinical studies as defined in 21 CFR Part 54.

VI. Integrated Review of Efficacy

There are no new efficacy data contained in this application. For the efficacy data of omeprazole magnesium 20 mg tablets, refer to the reviews of the original Rx-to-OTC NDA submission.

VII. Integrated Review of Safety

Omeprazole was first marketed for clinical use in Europe in 1988, and in the United States in 1989. The omeprazole magnesium MUPS tablet formulation, first launched in Europe (Sweden) in February 1998, is currently available by prescription worldwide in 33 countries. To date, the MUPS tablet is available as an OTC product in Sweden only.

The global post-marketing experience of omeprazole was reviewed by HFD-180 at the time of the original Rx-to-OTC switch NDA submission. The Integrated Summary of Safety (ISS) in the original NDA for Prilosec OTC (omeprazole magnesium delayed-release tablets), submitted January 27, 2000, included safety data that were available to AstraZeneca LP (AZLP) and The Procter & Gamble Company (P&G) through June 30, 1998 from clinical trials from the over-the-counter (OTC) development program with omeprazole magnesium MUPS tablets, clinical trials from prescription omeprazole capsules and prescription omeprazole post-marketing surveillance data.

Supplemental surveillance data was presented in the following submissions:

- 4-Month Safety Update Report, submitted May 25, 2000.
- August 28, 2000 Response to FDA's Request for Additional Information including:
  (1) OTC omeprazole magnesium clinical trial adverse events (AEs) available from July 1, 1998 through December 31, 1999 from P&G studies 1999017, 1999018, 1999019, and 1999022 and
  (2) worldwide omeprazole magnesium MUPS tablet postmarketing surveillance data of serious and non-serious AEs available from launch (February 1998) through December 31, 1999.
- Safety Update Report included in the February 12, 2002 NDA Resubmission containing:
  (1) outstanding safety information on omeprazole magnesium including an update of the worldwide post-marketing data for omeprazole magnesium MUPS

tablets from January 1, 2000 through June 30, 2001 and
(2) safety data obtained from P&G Actual Use study 2001007.

This review will cover safety data submitted by the sponsor in their latest December 20, 2002 submission. It contains an international post-marketing experience with Ome-Mg tablet from July 1, 2001 through September 30, 2002.

International Post-Marketing Experience with Ome-Mg from July 1, 2001 Through September 30, 2002.

This safety update report provides all worldwide serious post-marketed prescription omeprazole magnesium MUPS tablet AE information reported to AZLP from July 1, 2001 through September 30, 2002 from countries where the tablet formulation is marketed. No additional clinical trial adverse event data is included in this safety update report as there have been no additional OTC omeprazole magnesium clinical trials conducted during the reporting period. The omeprazole magnesium MUPS tablet referenced in this section is the omeprazole magnesium tablet formulation used in the OTC clinical studies submitted in NDA 21-229.

To update the post-marketing surveillance information provided previously, AZLP's current global safety database, Clintrace, was searched for the following types of serious adverse events (SAE) spontaneous reports received from July 1, 2001 through September 30, 2002 with the key ingredient of omeprazole and a unit dose form of MUPS tablet:

- All serious reactions from spontaneous notifications
- All serious reactions from literature
- All serious reactions from regulatory authorities or national drug monitoring centers

All SAE reports associated in time with omeprazole magnesium MUPS tablet treatment irrespective of indication or causality assessment are included in this summary. This includes reports with very limited information (e.g., inquiries from doctors and pharmacists), provided they contain minimum information required for a report, i.e., an identifiable patient, source, drug and adverse reaction.

Serious (Fatal and Non-Fatal) Post-Marketing Adverse Events
A total of 40 SAE (38 non-fatal and 2 fatal) cases comprising 75 total AEs were reported for omeprazole magnesium MUPS tablets worldwide during the reporting period. The 2 fatal cases are summarized below:

Case# 2001SE07747. A report was received from a Dutch health authority concerning a mentally retarded patient who swallowed 20 tablets of Losec MUPS (omeprazole) in several days. Subsequently severe liver function disturbances, nausea, vomiting and upper abdominal pain occurred and the patient also developed heart failure. The patient was hospitalized for thirteen days. It is unclear whether the heart failure was pre-existent. Liver enzymes were normal. [redacted] Concomitant medications were carbamazepine and diphantoine (phenytoin sodium). The liver function disturbances

were considered to be related to either omeprazole or carbamazepine. The patient died of heart failure several months later.

Case# 2001PK01152. A report was received from the Center for Documentation of Severe Skin Reactions in Germany via the German Health Authority (BfArM) concerning a 44-year-old male patient who died from Stevens-Johnson syndrome. The patient's medical history consisted of atrial fibrillation and malignant lymphoma (first diagnosed in 1997) with hepatic and renal infiltration. On ——— the patient was hospitalized because of hypercalcaemia, weakness, slurred speech and hallucinations. On ——— an acute gastroenteritis occurred with diarrhea and fever. On ——— sepsis and renal failure were diagnosed and on ——— pneumonia was suspected and oral candidiasis was diagnosed. On the next day, ——— the patient developed erythema, which was regressing two days later. On ——— however, there was a confluent exanthem on the patient's back, which spread to a generalized macular exanthem. On ——— blisters appeared on oral mucosa, lips, shoulders and upper arms with beginning epidermolysis. These were followed by genital erosions and conjunctivitis on ——— The patient died from multiple organ failure on ——— No autopsy was performed. Between ——— and ——— the patient had been treated with 43 different drugs. Assessed as related to the Stevens-Johnson syndrome were 26 of these drugs, including Antra MUPS (omeprazole magnesium), Beloc-Zok (metoprolol succinate) and Meronem (meropenem). However, according to the experts from the reporting documentation center allopurinol, Tazobac (piperacillin and tazobactam), ibuprofen and piperacillin are the drugs that most likely had been causative.

Table 3 displays all 38 serious non-fatal patient cases by system organ class. The table presents counts of each occurrence of a particular AE. A single patient case may have more than one AE occurring within one, or perhaps among more than one, system organ class. Therefore, the numbers of AEs does not coincide with the total number of cases.

Table 3. Adverse Events Reported for MUPS by Body System (7/1/2001-9/30/2002)

Body System	Number of AEs
Blood & lymphatic system disorders	7
Congenital, familial and genetic disorders	1
Ear & labyrinth disorders	1
Eye disorders	8
Gastrointestinal disorders	6
General disorders & administration site conditions	5
Hepato-biliary disorders	4
Immune system disorders	1
Infections & infestations	1
Investigations	4
Metabolism and nutrition disorders	1
Musculoskeletal, connective tissue & bone disorders	3
Neoplasms benign, malignant and unspecified	1
Nervous system disorders	5
Psychiatric disorders	4
Reproductive system and breast disorders	1
Respiratory disorders	4
Skin & subcutaneous tissue disorder	10

Comments:
The safety database provided by the sponsor in the current submission is relatively small compared to the previous reports. The two reported fatal adverse events probably were not directly related to omeprazole; there were confounding factors in both of the fatal cases, so a causative relationship to omeprazole cannot be determined.

The reported serious adverse events are consistent with the previously reported safety profile of omeprazole magnesium tablets with one exception. Visual disturbances or eye related adverse events are not listed in the Prilosec capsule prescription label. There are 8 eye-related adverse events occurring in 5 patients reported in the current safety update. Individual case reports have been reviewed. Two events in two patients, mydriasis and optic ischemic neuropathy could possibly be attributable to the use of omeprazole. The 3 other patients had many confounding factors and, therefore, the causal relationship to omeprazole cannot be assessed. A few non-serious adverse event reports related to visual disturbances were noted in the past safety data submissions. Visual disturbance seems to be a rare occurrence considering the wide extent of use of the drug.

Overall, the safety data presented in this NDA resubmission does not present signals to suggest that Prilosec OTC would be unsafe for OTC marketing. The safety of Prilosec has been well established by clinical trials supporting its approval as a prescription product, and by a long post-marketing experience.

VIII. Dosing, Regimen, and Administration Issues

The drug facts portion of the labeling proposed for the OTC marketing is presented in Attachment 1. The sponsor is proposing to market 3 different sizes of Prilosec OTC

packages: 1, 2 or 3 courses of therapy in 14, 28 or 42-count packages, respectively. To ensure consumer understanding of these different sizes of packages, the sponsor is proposing:

- Additional wording on the principal display panel indicating that the 14, 28 and 42-count package contains 1, 2, or 3 courses of treatment, respectively.
- Additional wording in the package insert explaining the package sizes.
- Development of unique packaging for the 28 and 42 count size products that places either 2 or 3, 14-count packages, respectively, in an outer carton that is labeled for the number of courses of therapy each package contains.

The sponsor is also proposing to provide not-for-sale 2-count sample starter kits to consumers with frequent heartburn, health care providers, and pharmacists in order to introduce Prilosec OTC. All samples will consist of a card with 2 pouches, containing 1 tablet of Prilosec OTC per pouch. The card will state that this is a starter kit with free samples and that these samples are to be followed with a 14-day regimen of Prilosec OTC. The back of the card will contain the full label instructions in a Drug Facts format. The package insert will accompany all samples.

Health care provider samples will be provided to physicians and pharmacists. Physicians will receive samples either by detailing or direct mailing. Pharmacist samples will be mailed directly to the pharmacists. The package insert and educational counseling materials will accompany samples. Pharmacists will be instructed to provide the samples to those patients, who in their judgment, are frequent heartburn sufferers. Pharmacists will also be instructed that the samples are not for general distribution.

Consumers who are pre-identified with frequent heartburn will receive one direct mailing of a 2-count product sample during the market introduction of the product. A frequent heartburn consumer mailing list is being developed using a survey containing questions about heartburn history and some general demographics. Consumers, who fulfill one of the following two criteria will be included on the mailing list:

1) suffer heartburn 2 or more days a week and/or
2) use heartburn medication with a frequency that indicates frequent heartburn.

The sponsor is proposing the same drug facts labeling and a package insert for all the different package sizes. The packages will differ only in their principal display panels (PDP).

Comments:
The proposed different packaging sizes were reviewed by the Agency and discussed with the sponsor during the October 9, 2002 End-of-Review meeting. The concept of marketing of these different sizes of Prilosec OTC packages was found to be acceptable by the Agency. Also, the screening survey to be used for the identification of patients with frequent heartburn was reviewed and found to be acceptable.

The discussion of the content and formatting of the proposed labeling is presented in this document after the review of the label comprehension study. In addition, an

interdisciplinary scientist will review the proposed labeling for compliance with the Drug Facts Labeling Rule.

Label Comprehension Study #22103 Review

This was a multi-center, label comprehension study to evaluate consumer comprehension of OTC labeling options for omeprazole magnesium tablets.

The study was conducted as a follow-up to previously conducted label comprehension studies on omeprazole magnesium tablets, the Food and Drug Administrations (FDA) feedback in the August 8, 2002 Action Letter, and the October 9, 2002 End-of-Review meeting.

Objectives

To evaluate how well consumers with heartburn understand the conditions (i.e., uses, warnings and directions) under which Prilosec OTC can be used based on their reading of the carton label. Consumer comprehension of three different package labels was investigated so that optimal labeling could be determined for OTC labeling.

Comprehension scores across the three labels were compared to determine which label was most effective in communicating key product information and the concepts identified by the FDA in the August 8, 2002 Action Letter:

1. The product is intended for those who experience frequent heartburn, and that it is not intended for the immediate treatment of heartburn, or the prevention of episodic (meal-induced) heartburn ("Uses" section).
2. The product should not be used for more than 3 courses of treatment in one year and there should be at least a 4-month period between courses.
3. The product should not be used for more than 14 days in a row unless directed by a doctor ("Directions" and "Warnings" sections).
4. Consumers understand when they should not use the product or when they should contact a doctor prior to use ("Warnings" section).
5. Consumers understand that "for some, it may take 1 to 2 days for the full effect" ("Uses" section in Label C).
6. Consumers understand not to chew the tablet or crush the tablet in food ("Directions" section).

To assess these concepts, the protocol outlined the following key communication objectives:

1. Product Use
    a) Product intended for treatment of frequent heartburn and not for episodic use.
    b) "may take 1-2 days for full effect"
2. Episodic and Frequent Heartburn Scenarios
    a) Product intended for treatment of frequent heartburn and not for episodic use.
    b) "may take 1-2 days for full effect"
3. Self-Selection
    a) Product intended for consumers with frequent heartburn and not for those with infrequent heartburn.

4. Label Warnings

a) Who cannot use Prilosec OTC ***("Do not use")***. Do not use if you have
- trouble or pain swallowing food
- vomiting with blood
- bloody or black stools

b) Who must first ask their doctor before using Prilosec OTC ***("Ask a doctor before use if you have")***. Ask your doctor before use if you have:
- [redacted] This may be a sign of a more serious condition.
- had heartburn over 3 months
- heartburn [redacted] with lightheadedness, sweating or dizziness
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent chest pain
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting

5. Directions

a) First Course of Treatment
- [redacted]
- take every day for 14 days
- do not take more than 1 tablet [redacted]

b) Repeated Courses (if needed)
- you [redacted] repeat a 14-day course of therapy every 4 months
- [redacted]

c) Other Directions
- Do not chew tablets
- Do not crush tablets in food.

Comments:
The sponsor correctly identified the most important areas of the label to be tested. The label tested in the previous label comprehension study #02255 failed to convey adequately that Prilosec is not for acute symptom relief or for prevention of meal-induced heartburn. Data showed that only 48% to 55% of consumers understood that omeprazole is not for episodic heartburn relief, and between 54% to 61% understood that it is not for episodic (meal-induced) heartburn prevention. These results prompted the Advisory Committee members to request a new label and a label comprehension study.

Study Design

This was a 3-arm (3 label version) study conducted among four cohorts of consumers based on literacy and heartburn frequency. Each cohort was projected to include approximately 450 consumers, with 150 assessing each of the 3 labels.

Study Location
Fifty-two (52) marketing research agencies located in geographically dispersed markets across the United States were used to complete recruiting and enrollment into this study. Forty of the sites conducted interviews via a shopping mall method (all 4 cohorts). In addition, 12 other sites (7 additional cities) conducted low literate interviewing. Low literate recruiting was conducted in facilities thought to have an enriched population of low literate adults.

Study Population
The population for this study consisted of adult males and females, 18 years of age and older who suffered from heartburn in the past 6 months.

For interviews conducted in shopping centers, shoppers were intercepted and screened for qualifications. The screening questionnaire included age information, some basic market research screening questions, and whether the subject had suffered from heartburn in the past 6 months. Consumers who qualified were taken to the site facility in the mall where they participated in the interview. Subjects from locations chosen to enrich the cohorts with low literacy were intercepted and screened for qualifications, and those who qualified were escorted to an interviewing area where they participated in the interview.

Inclusion Criteria
Cohort 1: Literate Consumers with Frequent Heartburn (n=450)

- Males or females, of any race, at least 18 years of age, with a mix of U.S. population demographics
- Score of 61 or higher on the Rapid Estimate of Adult Literacy in Medicine (REALM) test of literacy in medicine.
- 2 or more days per week with heartburn or taking prescription heartburn medication 2 or more days per week.

Cohort 2: Low Literate Consumers with Frequent Heartburn (n=450)

- Males or females, of any race, at least 18 years of age, with a mix of U.S. population demographics
- Score of 60 or lower on the REALM test of literacy in medicine
- 2 or more days per week with heartburn or taking prescription heartburn medication 2 or more days per week.

Cohort 3: Literate Consumers with Infrequent Heartburn (n=450)

- Males or females, of any race, at least 18 years of age, with a mix of U.S. population demographics
- Score of 61 or higher on the REALM test of literacy in medicine
- Less than 2 days per week with heartburn and taking prescription heartburn medication less than 2 days per week.

Cohort 4: Low Literate Consumers with Infrequent Heartburn (n=450)

- Males or females, of any race, at least 18 years of age, with a mix of U.S. population demographics

- Score of 60 or lower on the REALM test of literacy in medicine
- Less than 2 days per week with heartburn and taking prescription heartburn medication less than 2 days per week.

Exclusion Criteria

Subjects in all cohorts were excluded from the study if they:

1. Or anyone in their household worked in marketing research, for an ad agency/public relations firm, for a pharmaceutical company as a healthcare professional, or as part of a health care practice (for example a receptionist in a doctor's office) or for the FDA.
2. Participated in a marketing research study regarding healthcare products in the past 3 months.
3. Normally wear corrective lenses, contacts or glasses to read and did not have them with them.

Screening and Randomization

Once the screening questionnaire was completed, a REALM test for literacy in medicine was administered to all respondents to determine level of literacy. In addition, information on heartburn frequency and medications were collected. From this information, each subject was classified into one of the 4 cohorts described above and randomly assigned to read one of the three package labels for Prilosec OTC. Before the interview began, and during the course of the interview, respondents were told that they could refer to the package label at any time.

Comments:

Study subject recruitment methodology used for the study is acceptable. The screening questionnaire used in the study is acceptable.

Qualified consumers were randomized to one of the three labels (see Attachment 2). Each of the 40 main facilities received a randomization schedule in blocks of 3 for each of the 4 cohorts. Within each cohort, consumers were assigned to a label sequentially as they enrolled. This enabled each facility to have approximately equal numbers of consumers assessing each label within each of the 4 cohorts. The additional 12 low-literate facilities were provided with randomization schedules (in blocks of 3) for each of the two low literate cohorts. The projected sample size for each of the 4 cohorts was 450 with approximately 150 subjects assigned to each of the 3 labels.

Each consumer only saw one label. Each of the labels was printed on a carton, which was of the size and color of the actual market-ready carton.

Label Differences

Uses Section:

The three labels tested used different wording to convey the concept that the product is not intended for episodic use. The following table outlines the differences in the Uses section across the three labels:

Table 4. Differences Between the Three Tested Labels (Uses Section)

Label A	Label B	Label C
• for treatment of frequent heartburn	• same as Label A	• same as Label A
• only for those who suffer heartburn 2 or more days a week	• same as Label A	• same as Label A
• not intended for those who suffer occasional heartburn	• not intended for those who suffer heartburn fewer than 2 days per week	• not intended for: - immediate relief of heartburn - prevention of heartburn brought on by certain food or beverages
See package insert for more information	See package insert for more information	• for some, it may take 1-2 days for full effect

Warnings and Directions:
To convey the concept that the product should not be used for more than 3 courses of treatment in one year with at least a 4-month period between courses, two main variations in the directions and/or warnings were used in the labels.

Label A utilized a format in which the directions were divided into two subsections to make it clear to the consumer how to take the product for the first course of treatment, and how to take the product for additional courses of treatment, if needed.

Label B also utilized the same format as Label A and had additional wording in the "Stop use and ask a doctor if" section to further emphasize appropriate repeat usage and doctor intervention.

Label C utilized a "Bullet Point List" format, which listed the directions for the initial treatment regimen of 14 days in bullet points. Instructions for repeat product usage, if needed, were under the "Stop use and ask a doctor if" section of the label.

Questionnaire
The main questionnaire for the interview consisted of open and closed-ended questions as well as scenarios. Several "dummy" questions were interspersed throughout the questionnaire to avoid a series of questions with all the same response. Scenarios were written in "third person" to avoid respondents taking into consideration aspects of their own situation not relevant to the question. Consumers were told to consider what the person in the pretend situation should do or not do based on the label. Interviewers read the questions/scenarios to the respondents and the questions/scenarios were written on cards that the subjects read along with the interviewer.

Respondents were asked questions about the label to determine if they appropriately self-selected the product, recognized the product was only for frequent heartburn, and

comprehended the product label warnings and directions. Comprehension scores across the three alternative package labels were compared to determine which label and/or label section was most effective in communicating key product information and concepts.

Comments:
Only the drug facts portion of the three labels differed. A package insert was not tested in this study.

A detailed review of the questionnaire will be provided by the reviewers in the Division of Surveillance, Research, and Communication Support (HFD-410).

Study Dates
The study started the week of October 14 and ended the week of October 21, 2002.

Sample Size
Table 5 contains sample size/error calculations for the percentage of subjects with a correct/acceptable response, by Label and by Literacy or Frequency within Label. A worst case scenario was used which hypothesized a percentage of subjects with correct/acceptable responses of 50%.

Table 5. Sample Size/Error Calculation for Each Population

Population	Sample Size	Error at 95% Confidence Interval
By Label (A,B,C)	600	+/- 4%
By Literacy or Frequency within Label	300	+/- 6%

Data Management and Analyses
The completed questionnaires were shipped from the sites to [redacted] for data entry. All data were entered using a double data entry verification process. All verbatim responses were coded, reviewed, and classified into appropriate codes.

Two coding coordinators reviewed the verbatim comments and created "codes" for each unique verbatim comment. Consistency between the 2 coders was verified by the 2 coders independently coding three questions. After all responses were coded, any discrepancies between the two coders were resolved by an independent third party rater. Prior to starting data tabulation, principles for categorizing the codes from each question into "correct," "acceptable," and "incorrect" responses were determined. Once the coding process was completed, the codes were reviewed and assigned "correct", "acceptable", or "incorrect" responses. In some instances, "other" was assigned if the code was somewhat vague. For these instances, the respondents' first response to the question was used to determine the final classification.

A "correct" response was typically defined as either a response that was initially answered correctly or one that was initially not a correct response, but a follow-up question indicated correct action. An "acceptable" response was defined as a response

that was not what the label directs, but would not be incorrect in terms of product usage. In some cases, an "acceptable" response was also one in which the initial response was not correct, but a follow-up question indicated the respondent clearly understood the label. An "incorrect" response was defined as a response that indicated the subject did not understand the label.

After categorizing the codes, summary tables were constructed that contained the number and percentage of "correct", "acceptable" and "incorrect" responses to each question for all of the study populations. In general, the "correct" and "acceptable" were combined and indicate positive label comprehension, while the "incorrect" responses indicate negative label comprehension.

Statistical Analyses

The primary endpoints were the percentage of respondents who provided a correct/acceptable response based on reading the package label for each question/set of questions that corresponded to the objectives.

For each label, the percentage of correct/acceptable responses was presented for each of the 4 cohorts (frequent/literate, frequent/low literate, infrequent/literate, infrequent/low literate) for each of the questions/set of questions that address the communication objectives. For statistical testing and summarizing, each label was treated as a separate entity in terms of investigating each objective or section of the label.

In order to determine which sections of the label were best understood, the following analyses were carried out on the above endpoints.

1) A logistic regression was run to see the impact of Literacy (Literate vs. Low Literate) and Frequency (Frequent vs. Infrequent) on each Label wording understanding. The analysis was based on the percentage of consumers who provided a correct or acceptable response. The logistic model included the following independent factors:

LABEL (A, B, or C),
FREQUENCY (frequent or infrequent sufferer),
LITERACY (literate or low literate sufferer),
FREQUENCY*LITERACY,
LABEL*FREQUENCY, and
LABEL*LITERACY

The two interaction terms with LABEL (LABEL*FREQUENCY and LABEL*LITERACY) were investigated to determine if the understanding of the labels is different for Frequent and Infrequent heartburn consumers as well as for Literate and Low Literate consumers. The by-Frequency and by-Literacy percentages from each label were used to explain any interactions that occurred. If the LABEL*FREQUENCY and LABEL*LITERACY terms as described above were not significant ($p > 0.10$) in the above model, then the analysis in #2 below was carried out.

2) A Cochran-Mantel-Haenszel chi-square test with FREQUENCY and LITERACY as the stratification variables was carried out on each question/set of questions to determine

which label was best understood (across both literacy and frequency groups) for each section of the label. Hypotheses were tested separately on each label pair. The by-label percentages of correct/acceptable were used to prioritize the labels and/or label sections.

The statistical plan did not include carrying out all pair wise label comparisons within each of the four cohort groups. This was done intentionally in order to minimize the risk of finding statistical results that were significant just by chance due to the large number of comparisons. However, some by-label pair wise comparisons within the Low Literate and/or Infrequent groups were carried out. These were done because the LABEL*LITERACY and/or LABEL*FREQUENCY interactions were statistically significant making the overall by-label comparisons difficult to interpret; and because the Low Literate and Infrequent groups are of particular importance in this study.

Comments:
The target comprehension and threshold rates were not predetermined. No confidence intervals were provided for the data analyses of the study. Statisticians will be reviewing the statistical data analyses of the study.

Results

Subject Disposition
Table 6 below provides the number of respondents in each of the study cohorts, in total and by label.

Table 6. Number of Subjects in Each of the Study Cohorts

	Cohorts				
	Literate Frequent	Low Literate Frequent	Literate Infrequent	Low Literate Infrequent	Total
Total	**N=456**	**N=480**	**N=450**	**N=456**	**1842**
Label A	N=153	N=163	N=150	N=151	617
Label B	N=153	N=162	N=150	N=153	618
Label C	N=150	N=155	N=150	N=152	607

Demographics
Table 7 summarizes demographic characteristics of the participants.

Table 7. Demographic Characteristics of the Study Subjects

		% of Subjects (N=1842)
Gender	Male	46%
	Female	54%
Age	18-34 years	46%
	35-54 years	39%
	55 years or older	15%
Race	Caucasian	56%
	African American	32%
	Hispanic	7%
	Other	5%

The respondents in this study were made up of 46% male and 54% female, with 56% Caucasian, 32% African American, 7% Hispanic and 5% representing other races. Almost half of the respondents (46%) were between the ages of 18 and 34 years; 39% were 35-54 years and 15% were 55 years or older. The distribution of gender, age and race within each of the labels were similar to the overall distribution. Of the 1842 subjects in this study, 67 (4%) were currently taking prescription Prilosec, 109 (6%) were taking Pepcid, 111 (6%) were taking Zantac, and 77 (4%) were taking Prevacid. All other prescription heartburn medications were being used by less than 3% of consumers. The top three over the counter heartburn medications were Tums (31%), Rolaids (18%) and Pepto Bismol (14%).

Comments:
Demographically, the enrolled population was reasonably balanced in terms of age and gender, and captured a broad ethnicity spectrum. It is unclear whether the Pepcid and Zantac "currently used" were prescription, OTC or both.

For review purposes, the study results are presented according to the general outline of the Drug Facts labeling in Table 8 below.

Table 8. Presentation of Results per Drug Facts Labeling

Drug Facts Labeling	Objective	Concepts Comprehended Through OTC Labeling
Uses	Product Use Episodic/Frequent Use Self Selection	Product intended for treatment of frequent heartburn and not for episodic use.
Warnings	Label Warnings	When product should not be used. When a Doctor should be contacted prior to use.
Directions	How to use product	Take 1 tablet in the morning before breakfast every day for 14 days. Do not take more than 14 days unless directed by Doctor. Do not chew/crush tablets.

Product Use

Three questions were asked of the participants (two open-ended questions and a multiple choice question) to determine if consumers understood that the product was for "Treatment of Frequent Heartburn". Table 9 below displays results of the responses to the questions about the use of the product.

Table 9. Product Use

	Label A	Label B	Label C
% Correct/Acceptable:			
Product Uses (Qs 1 & 2)	99.5%	99.8%	99.3%
Treatment of Frequent Heartburn (Q 3)*	91.2%	91.4%	92.3%
% Reporting the following responses from Q3:			
Treatment of diarrhea	0.0%	0.0%	0.5%
Relief of constipation	0.5%	0.3%	0.3%
Immediate relief or prevention of occasional heartburn	7.9%	8.3%	7.2%
Something else	0.5%	0.2%	0.2%

*Respondents could select multiple responses to this question

From Table 9, nearly 100% of the respondents from labels A, B and C, respectively, correctly/acceptably identified Prilosec OTC as being a product for the "Treatment of Frequent Heartburn" when asked an open-ended question about the uses of the product (Qs 1 and 2). This was one of the few questions where the percentage of correct/acceptable answers was quite a bit larger than the percentage of correct answers. The sponsor's reason for this is that this question requested both "treatment" and "frequent" as responses to be considered a correct response. If only one was given, then the answer was considered only acceptable.

When given the opportunity to select the appropriate description of the product from a list of options (Q3), 91% of the respondents for Labels A and B and 92% from Label C correctly chose "Treatment of Frequent Heartburn". In addition, 8% of subjects from Labels A and B and 7% from Label C incorrectly selected "Immediate Relief or Prevention of Occasional Heartburn" as a use for this product. There were no significant differences between any pair of labels for these Product Use questions.

By-Literacy Results: Results of the responses to the questions about the use of the product stratified by literacy are presented in Table 10. There was no more than 1% difference (99%-100%) between Literate vs. Low Literate respondents for the percentage correct/acceptable for the open-ended Product Use question across all three labels. For the multiple-choice Product Use question (Q3), the literate respondents had percentages correct/acceptable between 94%-96%, while the low-literate respondents had lower percentages closer to 88%-89% across all three labels. Note that for the "Immediate relief or prevention of occasional heartburn" choice, there was a similar 5%-7% decrease in correct/acceptable answers from Literate to Low Literate across all labels.

Table 10. Product Use: Literate vs. Low Literate Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable:	Literate	Low Literate	Literate	Low Literate	Literate	Low Literate
Product Uses (Qs 1 & 2)	100%	99.0%	100%	99.7%	100%	98.7%
Treatment of Frequent Heartburn (Q 3)	94.1%	88.5%	95.4%	87.6%	96.0%	88.6%
% Reporting the following responses from Q3:						
Treatment of diarrhea	0.0%	0.0%	0.0%	0.0%	0.0%	1.0%
Relief of constipation	0.0%	1.0%	0.0%	0.6%	0.0%	0.7%
Immediate relief or prevention of occasional heartburn	5.6%	10.2%	4.6%	11.7%	4.0%	10.4%
Something else	0.3%	0.6%	0.0%	0.3%	0.0%	0.3%

Comments:
Overall, there was a good understanding of the use of the product. Between 91.2% and 99.8% of the subjects understood correctly that the product is for the treatment of frequent heartburn. The highest percentage of incorrect answers for the three label groups was about the use of the drug for relief and prevention of occasional heartburn. Even though there was no statistical difference, numerically Label C generated the fewest incorrect answers; this was not so when analyzed by literacy. In the low literacy subgroup overall comprehension scores were lower compared to that of literate subgroup.

By-Heartburn Frequency: As seen in Table 11, Heartburn Frequency did not appear to have an effect on the responses from the Product Use questions.

Table 11. Product Use: Frequent vs. Infrequent Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable:	Frequent	Infrequent	Frequent	Infrequent	Frequent	Infrequent
Product Uses (Qs 1 & 2)	99.1%	100%	100%	99.7%	99.0%	99.7%
Treatment of Frequent Heartburn (Q 3)	90.8%	91.7%	91.7%	91.1%	92.8%	91.7%
% Reporting the following responses from Q3:						
Treatment of diarrhea	0.0%	0.0%	0.0%	0.0%	1.0%	0.0%
Relief of constipation	0.3%	0.7%	0.3%	0.3%	0.7%	0.0%
Immediate relief or prevention of occasional heartburn	8.2%	7.6%	7.9%	8.6%	6.6%	7.9%
Something else	0.6%	0.3%	0.0%	0.3%	0.0%	0.3%

Comments:
There seems to be no difference in comprehension of the "Uses" of the product between frequent and infrequent heartburn sufferers.

Episodic and Frequent Use

Several scenarios (Qs 4/5, 6/7, 8/9, 10/11) were presented to the participants to determine if consumers understood that the product was not for episodic or infrequent use. The three labels tested had different wording under the Use section.

The percentages of correct/acceptable answers for the Frequent heartburn question (Qs 4 and 5) were 99%-99.5% for all three labels.

The three Episodic scenario questions gave percentages of correct/acceptable answers between 81% and 92%. For the "heartburn due to food" scenario (Qs 6 and 7), the percentage correct/acceptable was 84%-86% across the labels, and the "heartburn due to stress" scenario (Q 10 & 11) was 91%-92% across the labels. However, Label B had the highest comprehension of the "episodic prevention" scenario (Qs 8 and 9) with a correct/acceptable percentage of 86.1%, compared to 84.0% for Label A and 80.9% for Label C. Additionally, Label B was found to have a statistically higher percentage correct/acceptable than label C for this scenario ($p = 0.012$). The sponsor states that this also demonstrates that the additional wording on Label C, "*Not intended for prevention of heartburn due to food and beverages*", did not contribute to better comprehension of the "not for episodic use" concept. Table 12 displays the overall pairwise comparison results for the Episodic and Frequent Use scenarios.

Table 12. Infrequent/Episodic and Frequent Use

	Label A	Label B	Label C
% Correct/Acceptable			
Frequent Heartburn Scenario:			
Frequent Heartburn (Qs 4 &5)	99.2%	99.0%	99.5%
Infrequent/Episodic Heartburn Scenarios:			
Relief of infreq. symptoms due to food (Qs 6&7)	85.6%	85.4%	84.3%
Relief of infreq. symptoms due to stress (Qs 10&11)	91.1%	92.1%	90.6%
Episodic Prevention (Qs 8&9)	84.0%	86.1%	80.9%

By-Literacy: When broken out by literacy, there were only small differences ($\leq 1.3\%$) between Literate and Low Literate for the "frequent heartburn" scenario percentages. For the infrequent/episodic heartburn scenarios, the differences between Literate and Low Literate were larger, with the Low Literate respondents having a correct/acceptable percentage between 74%-88% and the Literate between 88%-97% across all labels. When inspected within Low Literate, Label B had a higher percentage correct/acceptable (by 2%-6%) for all three infrequent/episodic scenarios than Labels A and C. Table 13 below displays the results of infrequent/episodic scenarios comprehension among Literate and Low Literacy populations.

Table 13. Infrequent/Episodic and Frequent Product Use: Literate vs. Low Literate Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable	Literate	Low Literate	Literate	Low Literate	Literate	Low Literate
Frequent Heartburn Scenario:						
Frequent Heartburn (Qs 4 &5)	99.7%	98.7%	99.7%	98.4%	99.7%	99.3%
Infrequent/Episodic Heartburn Scenarios:						
Relief of infreq. symptoms due to food (Qs 6&7)	95.4%	76.1%	92.4%	78.7%	93.0%	75.9%
Relief of infreq. symptoms due to stress (Qs 10&11)	96.7%	85.7%	96.7%	87.6%	96.0%	85.3%
Episodic Prevention (Qs 8&9)	92.4%	75.8%	92.4%	80.0%	87.7%	74.3%

By-Frequency: Table 14 has the Episodic/Frequent scenarios broken out by heartburn frequency. The Frequent and Infrequent % correct/acceptable differed by less than 3% for Labels A and B. Label C had slightly larger differences between Frequent and Infrequent (0%-6%). Overall, there did not appear to be a consistent trend for Frequent versus Infrequent consumers across these scenarios. Sometimes the Frequent consumers comprehended better and other times the Infrequent consumers comprehended better. Additionally, the "heartburn due to food" scenario revealed a significant ($p = 0.09$) LABEL*FREQUENCY interaction indicating that Frequent and Infrequent consumers comprehend the labels differently. The Frequent consumers understood Label C best while the Infrequent consumers understood Label A best. However, when by-Frequency pair wise tests were carried out to determine label differences within the Frequent and Infrequent subgroups, no significant differences were found.

Table 14. Episodic and Frequent Product Use: Frequent vs. Infrequent Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable:	Frequent	Infrequent	Frequent	Infrequent	Frequent	Infrequent
Frequent Heartburn Scenario:						
Frequent Heartburn (Qs 4 &5)	99.1%	99.3%	99.4%	98.7%	99.3%	99.7%
Infrequent/Episodic Heartburn Scenarios:						
Relief of infreq. symptoms due to food (Qs 6&7)	84.5%	86.7%	86.7%	84.2%	87.5%	81.1%
Relief of infreq. symptoms due to stress (Qs 10&11)	90.2%	92.0%	92.7%	91.4%	93.1%	88.1%
Episodic Prevention (Qs 8&9)	83.2%	84.7%	85.7%	86.5%	79.3%	82.5%

Comments:
Data show that consumers understand well that Prilosec OTC is appropriate for the treatment of frequent heartburn. Comprehension that Prilosec OTC should not be used for the relief and/or prevention of infrequent/episodic heartburn was not as good, ranging from 84% to 92%. Comprehension scores in the low literacy cohorts were lower, ranging from 74% to 88%.

Based on the above results, Label B seems to the best in conveying the message. Label A and B had similar "Uses" section, so there is no surprise that they had very close comprehension scores. It is surprising that Label C was least understood. It is the only label that had a specific description about the mechanism of action, or the expectations from the drug. We could speculate that the Label C bulleted format of the "Uses" section interfered with comprehension. It reads:

- *for **treatment of frequent heartburn***
- *only for those who suffer heartburn 2 or more days a week*
- *not intended for:*
  - *immediate relief*
  - *prevention of heartburn brought on by certain foods or beverages*
- *for some, it may take 1-2 days for full effect*

When the "not intended for" section is separated from the main qualifier, one may assume that the drug is indicated for the two conditions listed under two indented bullets.

Question 10 was about the treatment of heartburn induced by stress. None of the labels had a warning about the use of Prilosec for stress-induced heartburn and therefore, the comprehension of this concept is irrelevant.

Self-Selection

One set of questions (Qs 12/13) was presented to the participants to determine if consumers understood whether the product was appropriate for them to take based on their heartburn frequency. The three labels tested had different wording for the Uses section, which covered the heartburn frequency requirement. Since respondents' heartburn frequency was directly linked to their selection of the product (e.g., a correct response for a Frequent sufferer was "Ok to take the product" whereas a correct response for an Infrequent sufferer was "Not Ok to take the product"), the Self-Selection results were broken out by Frequency. Table 15 below displays a summary of overall results for Self-Selection among frequent and infrequent heartburn sufferers.

Table 15. Self-Selection

	Label A	Label B	Label C
% Correct/Acceptable			
Frequent Heartburn Sufferers (Overall):	99.1%	99.4%	100.0%
Literate	100.0%	100.0%	100.0%
Low Literate	98.2%	98.8%	100.0%
Infrequent Heartburn Sufferers (Overall):	83.7%	82.2%	78.8%
Literate	92.7%	87.3%	87.3%
Low Literate	74.8%	77.1%	70.4%

From Table 15, over 99% of the Frequent heartburn sufferers provided a correct/acceptable response for Self-Selection on all three labels. Within the Infrequent group, 83.7%, 82.2% and 78.8% of the respondents from Labels A, B and C, respectively, correctly/acceptably identified that the product was NOT appropriate for them. There was a significant ($p < 0.001$) LABEL*FREQUENCY interaction indicating

that Frequent and Infrequent consumers comprehend the labels differently with respect to Self-Selection. The decrease in the Label C responses (78.8%) among the Infrequent group was the cause for the significant interaction. Moreover, when the pairwise comparisons were carried out separately for the Frequent and Infrequent groups, no statistical differences between the labels were found.

By-Literacy: When the Frequent and Infrequent groups are broken out by Literacy, the Literate sufferers have higher percentages correct/acceptable than the Low Literate sufferers for all labels. For the Infrequent/Literate subgroup, Label A had the highest percentage correct/acceptable of 92.7% compared to 87.3% for Labels B and C. In addition, for the Infrequent/Low Literate group, Label B had the numerically highest percentage correct/acceptable self selection of 77.1% compared to 74.8% for Label A and 70.4% for Label C.

Table 16 contains Self-Selection percentages broken out by Literacy only (averaging across Frequency levels). The Literate respondents had higher correct/acceptable percentages than the Low Literate respondents. Label A had the highest numerical response among the Literate group (96.4% for Label A, 93.7% for Labels B and C), and Label B had the highest among the Low Literate group (86.9% for Label A, 88.3% for Label B and 85.3% for Label C).

Table 16. Self-Selection: Literate vs. Low Literate Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable	Literate	Low Literate	Literate	Low Literate	Literate	Low Literate
Is this product OK for you to use? (Qs 12&13)	96.4%	86.9%	93.7%	88.3%	93.7%	85.3%

Comments:
Overall, results show that there was good self-selection among frequent heartburn sufferers. Between 98% to 100% of subjects irrespective of their literacy level, correctly self-selected. There was a statistically significant difference in self-selection between frequent and infrequent heartburn sufferers. The most self-selection errors were among the low literate infrequent heartburn sufferers (70% to 77%). Even though there was no statistical significance among the three tested labels, label B was the best understood by low literate infrequent heartburn sufferers. The results from the previous label comprehension study (#02255) had inferior results; only 67% of the subjects correctly answered self-selection questions. However, the self-selection assessment in study #02255 took into account not only the heartburn frequency, but also the contraindicated symptoms and contraindicated medications. Therefore, we cannot really assess if the new label has caused any improvement on the correctness of self-selection.

Warnings
Several scenarios (Qs 14/15, 16/17, 18/19, 20/21, 22/23, 29/30, 31, 32/33, 34/35) were presented to the participants to determine if consumers understood the product's label warnings. The label warning sections of the three labels had the same wording.

Among the seven Prilosec-specific label warning scenarios (warnings that actually appear on the label) six of them reported between 93%-99.7% correct/acceptable respondents across all labels. The only scenario, which was different from the others, was the scenario "frequent heartburn 2 or more days could be a sign of a more serious condition." The percentage correct/acceptable for this question was between 74%-77% across all three labels. The sponsor believes the "serious condition" question was not as well understood as the other Warning questions because of the fact that the words "acid reflux" appear on the labels for this warning, but were not included in the question.

For the 2 dummy questions (cold and constipation), between 92%-97% of the respondents provided a correct/acceptable answer across all labels. The constipation scenario was one of the few questions that had a rather large discrepancy between the percentage correct/acceptable and the percentage correct. The sponsor's reason for this is that since constipation is also a gastrointestinal condition (as is heartburn), many consumers responded that they would check with a doctor before taking the product, which was considered an "acceptable" response as opposed to "correct". Table 17 displays the results of responses to all Warnings.

Table 17. Label Warnings

	Label A	Label B	Label C
% Correct/Acceptable			
Do not use if you have:			
Trouble Swallowing food (Qs 32&33)	94.7%	93.2%	94.6%
Nausea and blood in vomit (Qs 34&35)	99.5%	99.7%	99.0%
Ask a doctor before use if you have			
Frequent heartburn caused by acid reflux, sign of serious condition (Q 31)	74.5%	73.7%	76.6%
Had heartburn over 3 months (Qs 14&15)	96.8%	96.8%	96.2%
Had heartburn with dizziness and lightheadedness (Qs 16 &17)	98.7%	99.0%	99.0%
Chest pain and shortness of breath (Qs 20&21)	98.2%	98.5%	98.8%
Chest pain and pain spreading to arms (Qs 29&30)	99.7%	99.2%	99.0%
Non-warning conditions("dummy" questions)			
Constipation (Qs 18&19)	92.2%	94.0%	92.3%
Cold (Qs 22&23)	96.8%	95.8%	95.9%

By-Literacy: When the percentage correct/acceptable is broken out by Literacy, the Low Literate scores are lower by 2%-5% for most label Warning questions as compared to the Literate scores (see Table 18). The Warning question regarding "heartburn with dizziness and lightheadedness" had a significant ($p < 0.001$) LABEL*LITERACY interaction. This was due to the fact that Label A had identical Literate and Low Literate percentages (98.7%) and Label B had identical Literate and Low Literate percentages (99.0%), but there was a difference, although small in magnitude, between Literate (100%) and Low Literate (98%) for Label C. In addition, the "chest pain and shortness of breath" scenario revealed a significant LABEL*LITERACY interaction ($p < 0.001$) driven by the fact that Labels A and C had bigger differences between Literate and Low Literate than Label B; although all were relatively small in magnitude.

Table 18. Label Warnings: Literate vs. Low Literate Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable	Literate	Low Literate	Literate	Low Literate	Literate	Low Literate
Do not use if you have:						
Trouble Swallowing food (Qs 32&33)	97.4%	92.0%	95.7%	90.8%	97.3%	91.9%
Nausea and blood in vomit (Qs 34&35)	99.7%	99.4%	99.7%	99.7%	99.7%	98.4%
Ask a doctor before use if you have						
Frequent heartburn caused by acid reflux, sign of serious condition (Q 31)	78.0%	71.2%	74.1%	73.3%	75.3%	77.9%
Had heartburn over 3 months (Qs 14&15)	98.0%	95.5%	97.0%	96.5%	98.0%	94.5%
Had heartburn with dizziness and lightheadedness (Qs 16 &17)	98.7%	98.7%	99.0%	99.0%	100%	98.0%
Chest pain and shortness of breath (Qs 20&21)	99.7%	96.8%	99.0%	98.1%	100%	97.7%
Chest pain and pain spreading to arms (Qs 29&30)	100%	99.4%	99.3%	99.0%	100%	98.0%
Non-warning conditions("dummy" questions)						
Constipation (Qs 18&19)	93.4%	91.1%	96.4%	91.7%	96.3%	88.3%
Cold (Qs 22&23)	98.3%	95.2%	97.4%	94.3%	96.7%	95.1%

By-Frequency: Overall, heartburn Frequency did not have a consistent affect across the Label Warning questions (see Table 19). For some warnings, the Frequent consumers had a higher percentage correct/acceptable than Infrequent, and for other warnings the reverse was true. The only warning that had a significant LABEL*FREQUENCY ($p = 0.09$) interaction was the "trouble swallowing food" scenario. This was due to the fact that for Labels A and B, the Infrequent consumers had a slightly higher % correct/acceptable than the Frequent (1%-2%); and for Label C the reverse was true: the Frequent consumers had a higher percentage (4%) than Infrequent. When the by-Frequency pairwise comparisons were carried out for this question, Label C (96.4%) had a statistically higher ($p = 0.031$) percentage correct/acceptable among the Frequent consumers than Label B (92.4%).

Table 19. Label Warnings: Frequent vs. Infrequent Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable:	Frequent	Infrequent	Frequent	Infrequent	Frequent	Infrequent
Do not use if you have:						
Trouble Swallowing food (Qs 32&33)	94.3%	95.0%	92.4%	94.1%	96.4%	92.7%
Nausea and blood in vomit (Qs 34&35)	99.7%	99.3%	100%	99.3%	99.0%	99.0%
Ask a doctor before use if you have						
Frequent heartburn caused by acid reflux, sign of serious condition (Q 31)	76.9%	72.0%	76.9%	70.4%	79.9%	73.3%
Had heartburn over 3 months (Qs 14&15)	96.5%	97.0%	96.5%	97.0%	95.7%	96.7%
Had heartburn with dizziness and lightheadedness (Qs 16 &17)	99.1%	98.3%	98.7%	99.3%	99.0%	99.0%
Chest pain and shortness of breath (Qs 20&21)	98.4%	98.0%	98.7%	98.3%	99.0%	98.7%
Chest pain and pain spreading to arms (Qs 29&30)	99.4%	100%	99.4%	99.0%	99.0%	99.0%
Non-warning conditions("dummy" questions)						
Constipation (Qs 18&19)	92.7%	91.7%	94.0%	94.1%	91.8%	92.7%
Cold (Qs 22&23)	97.2%	96.3%	95.9%	95.7%	94.8%	97.0%

Comments:
The warning section in all three labels tested was the same. This is reflected in the results of this section comprehension. Comprehension scores ranged from 93% to 99% among literate and from 71% to 99% among low literate subjects. There was no significant difference in comprehension of the warnings within any subgroups for all the three labels. One warning was not understood well:

This warning, as it is written, may be confusing to the consumer. It implies that the consumer is suppose to know if he/she is having heartburn due to acid reflux or due to some other reasons. The first part of this warning ( ) should be deleted. The second sentence "This may be a sign of a more serious condition" should follow the bulleted warning "Ask a doctor before use if you have had heartburn over 3 months".

Directions for Use
Study participants were presented a scenario and then asked questions to determine if they understood how to take Prilosec OTC (Qs 24-28, 36/37, 38/39, 40, 41, 42-45, 46/47, 48, 49, 50). Label A used one format for the directions; Label B used the same format, but with extra ' ' information under the Warnings section; and Label C used a bullet point format for the directions.

First Course

Most of the respondents assessing each label understood that they were to take the product in the morning before breakfast (87%-90%), and to take 1 tablet a day (95%-98%) for 14 days (94%-96%). In addition, across all 3 labels, 98%-99% of the respondents realized that they should not continue to take the product for more than 14 days (see Table 20). However, for the "number of tablets" question, Label A (97.5%) had significantly higher ($p = 0.013$) percentage correct/acceptable than Label C (94.8%).

Table 20. Directions for Use

	Label A	Label B	Label C
% Correct/Acceptable			
First course of treatment:			
Time of day to take product (Qs 38&39)	87.7%	89.6%	86.9%
Number of tablets to take each day (Q 40)	97.5%**	96.7%	94.8%*
How long to take product? (Q 41)	95.3%	96.2%	94.1%
Heartburn not gone after 14 days (Qs 24-28)	98.2%	99.0%	98.8%
Repeated courses:			
Heartburn returned 2 months after taking 14 tablets (Qs 42-45)	94.3%	94.5%	93.4%
Heartburn returned 6 months after taking 14 tablets (Qs 46&47)	97.9%	98.9%**	96.0%
How often can repeat 14-day regimen? (Q 48)	89.9%**	90.9%**	77.6%*¶
Time to reach full effect:			
Time to reach full effect (Q 50)	N/A	N/A	91.2%
Other directions:			
Do not crush tablets (Qs 36&37)	93.0%	94.7%	92.2%
Do not chew tablets (Q 49)	95.6%	95.3%	93.9%

* Statistically significant from label A; **Statistically significant from label C; ¶Statistically significant from label B

Repeated Courses of Treatment

On average, across the three "repeated treatment course" questions, Label B was numerically higher than Labels A and C. Specifically, for the "heartburn returned 2 months" question, Label B had a % correct/acceptable of 94.5%, followed by 94.3% for Label A and 93.4% for Label C. For the "heartburn returned 6 months" question, Label B (98.9%) was numerically higher than Label A (97.9%) and statistically higher ($p = 0.002$) than Label C (96.0%). The biggest difference between the labels occurred with the open-ended question for "how often to repeat a 14-day regimen". Labels A (89.9%) and B (90.9%) were statistically higher ($p < 0.001$) than Label C (77.6%).

Chew/Crush

There were also 2 directions "do not crush tablets in food" and "do not chew tablets" on all three labels. Between 92% and 96% of respondents correctly/acceptable responded that you should not chew or crush the tablets.

Time to Reach Full Effect

On Label C there appeared a statement in the Uses section, which stated '[redacted] Ninety-one percent of respondents who assessed Label C had a correct/acceptable response when asked, "How long might it take for this product to reach full effect?" According to the sponsor, this statement did not appear to increase the correct responses related to episodic scenarios due to the fact that Label C had the numerically lowest percentage correct/acceptable for all of the infrequent/episodic scenarios.

By-Literacy: Table 21 below contains the by-Literacy percentages correct/acceptable for the Direction questions.

Table 21. Directions for Use: Literate vs. Low Literate Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable	Literate	Low Literate	Literate	Low Literate	Literate	Low Literate
First course of treatment:						
Time of day to take product (Qs 38&39)	94.4%	81.4%	94.5%	85.0%	94.8%	79.5%
Number of tablets to take each day (Q 40)	99.3%	95.8%	99.0%	94.6%	98.6%	91.2%
How long to take product? (Q 41)	98.6%	92.3%	97.7%	94.9%	98.3%	90.2%
Heartburn not gone after 14 days (Qs 24-28)	99.0%	97.4%	99.7%	98.4%	100%	97.7%
Repeated courses:						
Heartburn returned 2 months after taking 14 tablets (Qs 42-45)	97.0%	91.7%	97.0%	92.1%	96.0%	90.9%
Heartburn returned 6 months after taking 14 tablets (Qs 46&47)	98.3%	97.5%	99.3%	98.4%	97.7%	94.5%
How often can repeat 14-day regimen? (Q 48)	96.4%	83.6%	96.0%	85.9%	83.9%	71.6%
Time to reach full effect:						
Time to reach full effect (Q 50)	N/A	N/A	N/A	N/A	94.6%	87.9%
Other directions:						
Do not crush tablets (Qs 36&37)	96.7%	89.5%	98.7%	90.8%	96.3%	88.2%
Do not chew tablets (Q 49)	98.7%	92.7%	99.0%	91.7%	98.3%	89.6%

For the "time of day to take product" question, the Low Literate consumers scored incorrectly approximately 10%-15% more often than the Literate consumers. However, for the other three First Course of Treatment questions, the differences between Literate and Low Literate percentage correct/ acceptable were smaller (1%-8%). There was a significant ($p < 0.001$) LABEL*LITERACY interaction for the "heartburn not gone after 14 days" question.

In addition, the open-ended "how often to repeat a 14-day course of therapy" question revealed a significant ($p = 0.039$) LABEL*LITERACY interaction. This was due to the fact that Label A was better understood by the Literate consumers for this question and Label B was better understood by the Low Literate consumers. When follow-up pairwise tests between labels were carried out for Literate and Low Literate separately, Labels A and B were both found significantly ($p < 0.001$) superior to Label C within the Literate and Low Literate groups. Label A was 12.5% higher in terms of percentage correct/acceptable than Label C for the Literate group and 12.0% higher than Label C in

the Low Literate group. Similarly, Label B was 12.1% higher than Label C in the Literate Group and 14.3% higher in the Low Literate group.

For the [redacted] question from Label C, the percentage correct/acceptable for Literate (95%) was higher than the Low Literate (88%). This was even more pronounced when the Low Literate group was further broken out by Frequency. Within the Infrequent consumers, the Low Literate group had lower comprehension (85%) than the Literate group (96%).

By-Frequency: According to Table 22 below, there do not appear to be any clinically meaningful differences between Frequent and Infrequent heartburn sufferers for the direction questions, including the [redacted] question for Label C. Sometimes the Frequent consumers had slightly better comprehension and other times the Infrequent consumers had slightly better comprehension of the directions.

Table 22. Directions for Use: Frequent vs. Infrequent Heartburn Sufferers

	Label A		Label B		Label C	
% Correct/Acceptable:	Frequent	Infrequent	Frequent	Infrequent	Frequent	Infrequent
First course of treatment:						
Time of day to take product (Qs 38&39)	86.6%	88.7%	89.6%	89.5%	89.6%	84.1%
Number of tablets to take each day (Q 40)	97.1%	98.0%	96.1%	97.3%	96.3%	93.2%
How long to take product? (Q 41)	95.1%	95.6%	96.1%	96.3%	94.3%	93.9%
Heartburn not gone after 14 days (Qs 24-28)	98.1%	98.3%	98.7%	99.3%	98.7%	99.0%
Repeated courses:						
Heartburn returned 2 months after taking 14 tablets (Qs 42-45)	93.4%	95.3%	95.6%	93.4%	93.8%	93.0%
Heartburn returned 6 months after taking 14 tablets (Qs 46&47)	97.25	98.7%	99.0%	98.7%	95.1%	97.0%
How often can repeat 14-day regimen? (Q 48)	89.6%	90.3%	90.7%	91.1%	78.5%	76.7%
Time to reach full effect:						
Time to reach full effect (Q 50)	N/A	N/A	N/A	N/A	92.0%	90.4%
Other directions:						
Do not crush tablets (Qs 36&37)	91.1%	95.0%	92.1%	97.4%	92.4%	92.1%
Do not chew tablets (Q 49)	94.9%	96.3%	94.6%	96.0%	95.7%	92.0%

There was a significant ($p < 0.084$) LABEL*FREQUENCY interaction for both the chew and crush questions. The reason for this is that the Infrequent heartburn sufferers understood Labels A and B better than Label C when it came to the chewing and crushing instruction, and Label C was better understood by the Frequent heartburn sufferers. When pairwise tests were carried out for the "do not chew" question, within the Frequent and Infrequent groups separately, Labels A and B had statistically higher ($p = 0.035$) percentage correct/acceptable than Label C within the Infrequent group (96.3% for Label A, 96.0% for Label B and 92.0% for Label C). Additionally, for the "do not crush" question, Label B was statistically superior ($p = 0.003$) to Label C within the Infrequent

consumers with a percentage correct/acceptable of 97.4% for Label B compared to 92.1% for Label C.

Comments:
The study results demonstrate that there was a good understanding of directions for use of Prilosec OTC. The Directions section on labels A and B were identical. Therefore, there is no surprise that these two labels did not differ in their comprehension scores of this section. Label C had a different format and was least understood. Comprehension rates of the Directions section for labels A and B ranged from 94% to 99% for literate and from 81% to 98% for low literate subjects. The concept of repeated courses of treatment, which was not included in the earlier label iterations, was well understood. Between 90% and 99% of subjects correctly answered questions about the frequency and the timing of repeated 14-day courses of Prilosec OTC.

The concept about the expectations of efficacy for Prilosec OTC was included on label C only. It was well understood by literate (94.6%) and low literate subjects (87.9%). This concept is not included in the proposed package label. The sponsor's argument for not including the statement is that it did not help to increase comprehension related to episodic heartburn scenarios. In the opinion of this reviewer, the concept about the expectations of full effect should be included on the drug label. Prilosec differs in its mechanism of action from the other currently available OTC heartburn medicines, and therefore, information about the expected effect is warranted.

Conclusions:
The label comprehension study was well designed and consistent with the Agency's request for information. The three tested labels gave insight as to what information was well understood, as well as about the weaknesses of the labels. With some modifications Label B seems to be the best choice for OTC marketing. It is able to communicate key medical information about Prilosec. Suggestions on how the information from the study could be used to enhance the final OTC label, are listed below.

Recommendations on the Proposed Prilosec OTC Label:
1. The "Uses" section of the label in addition to already listed 3 bullets, should include the following statements:

- _____
- *not intended for immediate relief of heartburn*

2. In the section "Ask a doctor before use if you have", the words _____ should be eliminated. The first and second bullets should be combined into one and rewritten as follows:

- *had frequent heartburn over 3 months. This may be a sign of a more serious condition.*

Comments on the Proposed Package Insert:
Concepts to be included in the package insert were discussed with the sponsor during the October 9, 2002 End-of-Review meeting. The sponsor correctly identified areas of

weaknesses of the proposed package insert. For the most part, the information provided in it is consistent with the Agency's request for information.

The following are the recommendations for improvement of the package insert:

1. The section "[redacted] should have the fourth bullet:

- *[redacted]*

2. In the section "Ask a doctor before use if you have", the first and second bullets should be combined into one and rewritten as follows:

- *had frequent heartburn over 3 months. This may be a sign of a more serious condition.*

3. In the section [redacted], the last sentence should be rewritten to: [redacted]

IX. Use in Special Populations

The sponsor did not request marketing of Prilosec OTC in subjects less than 18 years of age. Omeprazole use in pediatric population will remain under the prescription label. The package label appropriately directs consumers to consult a physician if the patient is under 18 years of age.

Omeprazole magnesium is a pregnancy category C drug. Issues with regard to the use of omeprazole magnesium by pregnant women have been addressed by HFD-180. The product label carries an appropriate pregnancy warning as specified in 21 CFR 201.63.

X. Conclusions and Recommendations

The sponsor fulfilled the Agency's request for information for the Prilosec OTC Rx-to-OTC switch.

Since Label B is well understood, Prilosec OTC (omeprazole magnesium) 20 mg tablet should be approvable as an OTC product for the treatment of frequent heartburn with the following modifications of the label and package insert:

1. The "Uses" section of the label in addition to already listed 3 bullets, should include the following statements:

- [redacted]
- not intended for immediate relief of heartburn

2. In the section "Ask a doctor before use if you have", on the label as well as on the package insert: eliminate the words "[redacted]The first and second bullets should be combined into one and rewritten as follows:

- had frequent heartburn over 3 months. This may be a sign of a more serious condition.

3. The section "[redacted] on the package insert should have the fourth bullet:

•

4. On the package insert, in the section [redacted], the last sentence should be rewritten to: [redacted]

No specific post-marketing studies are needed. The safety data submitted in this application did not present any safety signals that would preclude Prilosec from OTC marketing. Since a large uncontrolled population will be exposed to the drug after its Rx-to-OTC switch, post-approval safety should be vigilantly monitored, and submitted to the Agency as described in 21 CFR 314.50(d)(5)(vi)(b).

/S/

Daiva Shetty, M.D.
Medical Officer
Division of OTC Drug Products (HFD-560)

/S/

Andrea Leonard-Segal, M.D., M.S.
Team Leader
Division of OTC Drug Products (HFD-560)

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7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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Andrea Segal
4/25/03 03:38:15 PM
MEDICAL OFFICER

DEC 16 2002

OTC MEDICAL OFFICER'S REVIEW

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

IND #:	**54,307**
Drug name:	**Prilosec OTC (omeprazole magnesium)**
Sponsor:	**AstraZeneca LP**
	Procter&Gamble Company
Pharmacologic Category:	**Proton Pump Inhibitor**
Proposed Indications:	**For Prevention of Frequent Heartburn**
Dosage Form:	**20 mg Tablet**
Route of Administration:	**Oral**
Submission dates:	**November 20, 2002**
Review date:	**December 4, 2002**
Reviewer:	**Daiva Shetty, MD**

Introduction:
The sponsor has submitted material as part of their ongoing development program to switch Prilosec 20 mg from prescription to over-the-counter (OTC) status.

On October 9, 2002 the sponsor and the FDA held an end of review meeting. The following issues were discussed in the meeting: a draft protocol for a Label Comprehension Study, three proposed labels for final testing, a draft package insert, a new proposed trade name, a request for certain labeling changes, and a request for a waiver of the NDA safety update requirements.

In this November 20, 2002 submission the sponsor is requesting a meeting to discuss proposed commercial package sizes for Prilosec OTC, and a proposed program to distribute product samples to consumers with frequent heartburn and health care professionals. In addition, the sponsor is asking the Agency to comment on their revised package insert.

Commercial Package Sizes:
The sponsor is requesting to market 3 different sizes of Prilosec OTC packages: 1, 2 or 3 courses of therapy in 14, 28 or 42-count packages, respectively. To ensure consumer understanding of these different sizes of packages, the sponsor is proposing:

- Additional wording on the principal display panel indicating that the 14, 28 and 42-count package contains 1, 2, or 3 courses of treatment, respectively.

- Additional wording in the package insert explaining the package sizes.
- Development of unique packaging for the 28 and 42 count size products that places either 2 or 3, 14-count packages, respectively, in an outer carton that is labeled for the number of courses of therapy each package contains.

Product Sample Distribution:
The sponsor is also proposing to provide not-for-sale 2-count sample starter kits to consumers with frequent heartburn, health care providers, and pharmacists in order to introduce Prilosec OTC. All samples will consist of a card with 2 pouches, each containing 1 tablet of Prilosec OTC per pouch. The card will state that this is a starter kit with free samples and that these samples are to be followed with a 14-day regimen of Prilosec OTC. The back of the card will contain the full label instructions in a Drug Facts format.

Professional samples will be mailed or personally detailed to the target audience. Consumer samples will be mailed to consumers who meet the definition of the target population – heartburn 2 or more days a week. The consumers will be identified through a mailed survey in which they will be asked various questions about their heartburn experience, including the frequency of their heartburn, current medication regimen(s) and what behaviors they use to cope with their heartburn. Pharmacists prior to dispensing a starter kit will use the same survey on consumers. These samples will be mailed to consumers only once during the introduction period.

Comments:

1. The sponsor's proposal to market 1, 2, and 3 courses of treatment is acceptable. The statement indicating the number of treatment courses on the principal display panel (PDP) is not prominent enough. The sponsor should enhance the language on the PDP for multi-course treatment packages indicating the number of courses in the package.

2. In reference to 2-count sample starter kits, it is acceptable that they will be distributed to consumers identified as frequent heartburn sufferers, health care providers, and pharmacists. It is important not to send sample starter kits more than once because it may encourage consumers to use Prilosec OTC intermittently. The sponsor did not provide a sample of the survey to be used for the identification of consumers with frequent heartburn.

The labeling for these starter kits requires some modification:

- Because Drug Facts is on the back of the card and not on the PDP, the heading "— —" on the PDP should be deleted.
- The labeling should clearly explain the concept of 14-day therapy. This information should be communicated not only on the back of the card but also on the PDP.

Each 2-count sample pack should be dispensed with the approved package insert.

3. Comments on the proposed package insert.
The sponsor correctly identified the concepts that have to be addressed in the package insert. Detailed review and final approval of the labeling and the package insert will be done at the time of resubmission of the NDA.

Recommendations:

- X• Under the conditions outlined by the sponsor, it is acceptable to market up to three 14-day courses and two-tablet sample packs of Prilosec OTC.
- √• The sponsor should provide for the Agency review a copy of a survey sample to be used for the identification of consumers with frequent heartburn.
- √• The sponsor should improve the multi-course package label by enhancing the language on the PDP indicating the number of courses of therapy.
- √• The starter kit package PDP should clearly explain that appropriate use of Prilosec OTC requires 14 consecutive days of therapy. Each 2-count sample pack should be dispensed with the approved package insert.
- √• The title "Drug Facts" on the PDP of the sample package should be deleted. The sponsor should follow Labeling Requirements for OTC Drugs as specified in 21 CFR 201.66.

conveyed in 12/12/02 meeting w/ P&G

/S/

Daiva Shetty, M.D.
Medical Officer
Division of OTC Drug Products (HFD-560)

/S/

Andrea Leonard-Segal, M.D., M.S.
Team Leader
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MEDICAL OFFICER

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NOV 14 2002

OTC MEDICAL OFFICER'S REVIEW

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

IND #:	**54,307**
Drug name:	**Prilosec1 (omeprazole magnesium)**
Sponsor:	**AstraZeneca LP**
	Procter&Gamble Company
Pharmacologic Category:	**Proton Pump Inhibitor**
Proposed Indications:	**For Prevention of Frequent Heartburn**
Dosage Form:	**20 mg Tablet**
Route of Administration:	**Oral**
Submission dates:	**September 5, 2002**
	September 13, 2002
	September 17, 2002
	September 19, 2002
Review date:	**September 27, 2002**
Reviewer:	**Daiva Shetty, MD**

Introduction:
The sponsor has submitted material as part of their ongoing development program to switch Prilosec 20 mg from prescription to over-the-counter (OTC) status.

In the August 8, 2002 Action Letter the Agency requested the sponsor to revise labeling to include several concepts and conduct a new label comprehension study. Some of the concepts that were asked to be included in the labeling and tested in a label comprehension study are listed below:

1. Determine if consumers understand that omeprazole magnesium tablets are not intended for the immediate treatment of heartburn, or the prevention of episodic (meal-induced) heartburn.
2. Determine if consumers with heartburn understand that omeprazole magnesium tablets may take 1 to 2 days of use to work.
3. Determine if consumers with heartburn understand when to see their doctor before and after starting treatment.
4. Determine if consumers understand when to ask a doctor before use if they have any of the label warning symptoms.
5. Determine if consumers understand the label use directions.

This submission is the sponsor's response to the Agency's Action Letter dated August 8, 2002. It contains a draft protocol for a Label Comprehension Study, three proposed labels for final testing, a revised draft package insert, a new proposed trade name, request for certain labeling changes, and request for a waiver of the NDA safety update requirements.

This review will cover the proposed label comprehension study, and related materials (labels and package insert). The Division of Coagulation and Gastrointestinal Drug Products (HFD-180) will address the proposed trade name, drug-drug interaction issues, and the requirement for the NDA safety update. In addition, the Division of Surveillance, Research, and Communication Support (HFD-410) will comment on the proposed label comprehension study.

Review of the Label Comprehension Study Protocol

Title:
A Multi-Center, Label Comprehension Study to Evaluate Consumer Comprehension of OTC Labeling Options for Omeprazole Magnesium Tablets

Objective:
To evaluate how well consumers with heartburn understand the conditions (i.e. uses, warnings, and directions) in which they can use omeprazole magnesium tablets based on reading the carton label. Key communication objectives to be evaluated include the following:

1. Consumers with heartburn understand that:
   1) Omeprazole magnesium tablets is for adults who have frequent heartburn.
   2) Omeprazole magnesium tablets are not intended for relief/prevention of episodic heartburn.
2. Consumers with frequent heartburn understand when to see their doctor before and after starting treatment.
3. Consumers with frequent heartburn understand to ask a doctor before use if they have any of the label warning symptoms.
4. Consumers with frequent heartburn understand the label directions and when they can take an additional course of treatment without physician intervention.

Study Design:
This is 3-leg (3 label version) study to be conducted among four cohorts:

- Cohort 1: Literate Consumers with Frequent Heartburn
- Cohort 2: Low Literate Consumers with Frequent Heartburn
- Cohort 3: Literate Consumers with Infrequent Heartburn
- Cohort 4: Low Literate Consumers with Infrequent Heartburn

Qualified consumers will be randomized to one of three labels within each of the approximately 40 shopping facilities. Each facility will receive a randomization schedule by the Sponsor, which will be used to randomly assign consumers sequentially as they enroll.

Consumers will be asked to read one of three package labels for omeprazole magnesium tablets. Then they will be asked questions about the label to determine if they appropriately self-select the product, recognize the product is only for frequent heartburn, and comprehend the product label warnings and directions. Comprehension scores across three alternative package labels will be compared to determine which is most effective in communicating key product information.

Study Population:
The population for the study will consist of four cohorts of adult males and females, 18 years of age and older.

1. Literate Consumers with Frequent Heartburn (n=450, 150 x 3 label version legs). This population will be intercepted in shopping center malls and screened for participation.
2. Low Literate Consumers with Frequent Heartburn (n=450, 150 x 3 label version legs). This population will be intercepted in both shopping center malls and off-site locations (in lower socioeconomic environments) and screened for participation.
3. Literate Consumers with Infrequent Heartburn (n=450, 150 x 3 label version legs). This population will be intercepted in shopping center malls and screened for participation.
4. Low Literate Consumers with Infrequent Heartburn (n=450, 150 x 3 label version legs). This population will be intercepted in both shopping center malls and off-site locations (in lower socioeconomic environments) and screened for participation.

Inclusion Criteria:
Cohort 1: Literate Consumers with Frequent Heartburn
- Males or females, of any race, and at least 18 years of age, balanced to U.S. population demographics.
- Experiencing heartburn 2 or more days a week.
- Score 61 or higher on the REALM test of medical literacy.

Cohort 2: Low Literate Consumers with Frequent Heartburn
- Males or females, of any race, and at least 18 years of age, balanced to U.S. population demographics.
- Experiencing heartburn 2 or more days a week.
- Score 61 or lower on the REALM test of medical literacy.

Cohort 3: Literate Consumers with Infrequent Heartburn
- Males or females, of any race, and at least 18 years of age, balanced to U.S. population demographics.
- Experiencing heartburn less often than 2 days a week.
- Score 61 or higher on the REALM test of medical literacy.

Cohort 4: Low Literate Consumers with Infrequent Heartburn

- Males or females, of any race, and at least 18 years of age, balanced to U.S. population demographics.
- Experiencing heartburn less often than 2 days a week.
- Score 61 or lower on the REALM test of medical literacy.

Exclusion Criteria:
Respondents in all cohorts will be excluded from the study if they:

- Or anyone in their household works in marketing research, for an ad agency/public relations firm, a pharmaceutical company, as a healthcare professional, or as part of a health care practice (for example a receptionist in a doctor's office) or for the FDA.
- Participated in a marketing research study regarding a healthcare product in the past 3 months.
- Normally wear corrective lenses, contacts or glasses to read and do not have them with them.

Packaging and Labeling:
The labels will be market-ready cartons of omeprazole magnesium tablets. There will be three versions of the package label tested with each of the cohorts in this study.

Study Procedures and Assessments:
Recruitment for this study will take place in approximately forty (40) facilities located in shopping malls (to obtain all of the literate frequent heartburn sufferers and some of the low literacy frequent and infrequent heartburn sufferers) and approximately twelve (12) off-site locations targeted to obtain the majority of the low literacy frequent and infrequent heartburn population. All sites will be geographically dispersed throughout cities in the U.S. For interviews conducted in shopping centers, shoppers will be intercepted and screened for qualifications. Those who qualify will be escorted to the interviewing area in the off-site facility where they will participate in the interview. Regardless of the method of recruitment, all participants who meet all the study qualifications will be given the REALM test, and will then be asked to read the label.

Label Interview:
A marketing research interviewer from the site will have the respondent read one of the labels and then administer the label interview.

Qualified consumers will be randomized to one of three labels within each of the approximately 40 shopping facilities. Each facility will receive a randomization schedule by the Sponsor, which will be used to randomly assign consumers sequentially as they enroll. This should enable each facility to have approximately equal numbers of consumers per label.

Evaluation Criteria:

1. Demographics
Demographic information, such as the respondent's age, sex, education, income and race, will be recorded at the time of the interview.

2. Label Comprehension Interview
Questions will be asked to address each of the communication objectives listed under the Objectives section.

Statistical Methods and Analytical Plan
A respondent will be considered to have successfully met a particular communication objective if, after probing, she/he presents a correct/acceptable response to the questions) related to that objective.

The primary endpoints will be the percentage of respondents who provide a correct/acceptable response based on reading the label for the following criteria:

1. Product use: Omeprazole magnesium tablets is for the treatment of frequent heartburn.
2. Self-selection: omeprazole magnesium tablets is for frequent heartburn sufferers (experience heartburn 2 or more days a week) and not for infrequent heartburn sufferers (experience heartburn less often than 2 days a week).
3. Episodic/Frequent Use Scenarios: omeprazole magnesium tablets are for frequent heartburn sufferers and not for episodic use (e.g., not for relief/prevention of episodic heartburn).
4. Label Warning Scenarios:
   - Respondents know when to see their doctor before and after starting treatment.
   - Respondents understand to ask a doctor before use if they have any of the label warning symptoms, as demonstrated through direct scenarios.
5. Directions for Use Scenarios:
   - Users should take 1 pill each day in the morning before breakfast for 14 consecutive days.
   - Users should not use more than one 14-day course of therapy every 4 months unless directed by their doctor.
   - Users can take another course of therapy at 4-month intervals.
   - Users should notify their doctor if heartburn returns within 4 months of using omeprazole magnesium tablets for 14 days.
   - Users know not to chew or crush tablets before swallowing, or crush tablets in food.

For each label, the percentage of correct/acceptable responses will be presented for each of the 4 cohorts (frequent/literate, frequent/low literate, infrequent/literate, infrequent/low literate) for the above responses within each of the 3 labels. In order to determine which sections of the label are best understood, the following analysis will be carried out on the above endpoints.

1. A logistic regression will be run to see the impact of Literacy and Frequency on which Label is best understood.
2. If the label frequency and label literacy terms are not significant ($p > 0.10$) in the first model, then Cochran-Mantel-Haenszel chi-square test with "frequency" and "literacy" as the stratification variables will be carried out to determine which

sections of the label are best understood. The by-label percentages of correct/acceptable will be used to prioritize the labels and/or label sections.

Comments on the label comprehension study:

The sponsor correctly identified the issues to be addressed in a label comprehension study.

The recruitment method is acceptable for this kind of study.

Participants will be asked about their income. There is no reason to collect this information for the purposes of this study.

The three labels to be tested in the proposed label comprehension study have been reviewed. There are many deficiencies on each of the labels. The order and the content of subheadings are not in accordance with CFR 201.66. The interdisciplinary scientist assigned to the labeling review will give detailed comments on the format of the proposed labels.

Previous label comprehension, as well as actual use studies, showed that consumers understand well that omeprazole magnesium tablets are for the prevention of frequent heartburn, but did not understand well that they are not for the relief of acute heartburn symptoms or for the prevention of meal induced heartburn. About 1/3 to almost 1/2 of the subjects in the label comprehension studies stated that they would use the drug for acute relief or prevention of meal induced heartburn. Majority of the members of the joint meeting of the Nonprescription Drugs Advisory Committee and Gastrointestinal Drugs Advisory Committee on June 21, 2002, recommended including information about the expectations of efficacy of omeprazole magnesium tablets. Therefore, one of the Agency's requests in the Approvable Letter was to include in the labeling concepts that omeprazole magnesium tablets are not intended for the immediate treatment or the prevention of heartburn brought on by certain foods. The Agency also suggested including on the label concept that the drug may take 1 to 2 days to work. The sponsor is not agreeable to this request.

The labels proposed for the label comprehension study do not have information on how omeprazole magnesium tablets differ from the other heartburn medications currently available OTC. There is no information on the label that explains this difference. Including information about expectations of efficacy may be very useful to consumers for the effective use of the product. Therefore, the sponsor has to include a statement that omeprazole is not for immediate relief or prevention of heartburn brought on by food on at least one of the labels, and study comprehension of this concept. This information should also be included in the package insert of the product.

The three proposed labels look very alike. They should be different enough to express the main concepts in various ways to determine optimal labeling that best conveys the message.

The questionnaire for the study has been reviewed. A few deficiencies have been noted.
1. There are no questions about the expectations for the efficacy of omeprazole magnesium tablets.
2. Questions #17, 18, and 24 have been found to be too leading. All three questions are testing consumer understanding of label warnings, and have a wording "What else, if anything should you do now?" The better way to test if consumers understand that they should consult a physician if they have certain condition would be by asking more open questions such as "If you were this person (described in the situation), would you be able to use this product? Why do you say that?"

More detailed suggestions for the questionnaire will be provided by the reviewer from the Division of Surveillance, Research, and Communication Support (HFD-410).

Statisticians should assess the proposed analyses and the appropriate number of participants to enroll into the study so that it is adequately powered.

Comments on the revised package insert:
The information in the package insert is not consistent with the proposed labels. The package insert should carry all the warnings and directions listed on the proposed labels. The statements about the warning conditions and drug-drug interactions are very vague, e.g., [redacted] *. The sponsor has to list specific conditions with their symptoms, and all the medications that may cause interactions.*

Certain statements are promotional in tone and should be rephrased or deleted. For example, it states that [redacted] *This statement should be deleted. The first statement in the package insert states that* [redacted] *, but it does not explain how it is different. The sponsor may consider including information comparing mechanism of action of omeprazole with the other groups of heartburn medications. Statements about the expected efficacy should be included to better inform consumers.*

Other Comments:
The sponsor is requesting a waiver of an update of safety information. The last safety data submitted by the sponsor covered the time period from January 1, 2000 through June 30, 2001. At the time of the next resubmission of the NDA it will be at least 1.5 years since their last safety data update. Therefore, the sponsor should follow safety update requirement as set forth in 21 CFR 314.50 (d) (5) (iv) (b).

Conclusions:
In general, the label comprehension issues, to be studied in the proposed label comprehension study, are consistent with the Agency's request for information. Suggestions, how to improve the proposed study, labels, and the package insert are listed below.

Recommendations:

Labeling must be formatted in accordance with the requirements of 21 CFR 201.66.

The warning on the label A "See your doctor if: you have chest pain or shoulder pain with: shortness of breath, sweating, or pain spreading to arms, neck or shoulders", should be listed as a separate bullet.

The sponsor should include information about the expected efficacy of the product on the label and the package insert.

The proposed package insert has to be revised. The package insert at the very minimum needs to contain all of the "Drug Facts" information as written on the label. It has to list the warning conditions with their symptoms, as well as all drugs that may cause interactions with omeprazole magnesium. Information about how omeprazole magnesium is different in the onset of action, efficacy, and duration of effect compared to the other currently marketed OTC heartburn medications, should be provided for the consumer. Superiority statements should be deleted.

The following are suggestions for improvement of the proposed study protocol:

- *The three proposed labels should be different enough to express the main concepts in various ways.*
- *The label and the package insert should carry information about the expected efficacy of the drug. It should state that omeprazole tablets are not intended for the immediate relief of heartburn, or the prevention of heartburn brought on by certain foods or beverages.*
- *The sponsor should adequately test consumer understanding of the "Use" section of the label, including expectations for the efficacy of the product.*
- *Questions #17, 18, and 24 should be revised, as they are leading and could bias responses.*
- *The study should be adequately powered.*

The request for the waiver, to be exempt from the requirement for the NDA safety update, should be denied.

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

Concurrence:

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Daiva Shetty
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Charles Ganley
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MEDICAL OFFICER

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	ODS POSTMARKETING SAFETY REVIEW	
TO: Victor Raczkowski, M.D., Acting Director Division of Gastrointestinal & Coagulation Drug Products HFD-180	**FROM:** Ann Corken Mackey, RPh, MPH Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	**ODS PID #** D020248 June 11, 2002

DATE REQUESTED:	**REQUESTOR/Phone #:**	
DATE RECEIVED:		
DRUG (Est): Omeprazole	**NDA/IND #** 21-220	**SPONSOR**: AstraZeneca
DRUG NAME (Trade): Prilosec	**THERAPEUTIC CLASSIFICATION:**	

EVENT: Anaphylaxis

Executive Summary: This consult was prepared in response to a request from an HFD-180 medical officer to document anaphylaxis associated with omeprazole use, as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for reports of anaphylaxis received up to April 25, 2002; reports of anaphylaxis are discussed below.

Of the 17 unduplicated domestic cases of anaphylaxis (including two cases of anaphylactic shock) associated with omeprazole use reported through AERS, there were no fatalities. The symptoms reported included skin involvement (e.g., rash, hives), edema (e.g., eyelids, throat), dizziness, flushing, and dyspnea. Three reports described cardiovascular involvement (i.e., tachycardia, supraventricular tachycardia/ventricular bigeminy, tachycardia/elevated blood pressure). Two of the reports discussed in this case series were positive rechallenges. For five of the reports, the report images were not available (these reports were submitted as periodic reports and the case narratives were not available); therefore, little is known about these cases. In addition, three reports in this case series were submitted by consumers and the quality and completeness of the data were not as good as reports received from health care practitioners. Of the three reports of anaphylaxis identified in the medical literature, two of the events occurred with the injectable dosage form of omeprazole which is not available in the U.S; there were no fatalities.

The omeprazole labeling includes anaphylaxis and other related allergic reaction events (e.g., rash, angioedema, tachycardia, elevated blood pressure). Omeprazole is used extensively in the U.S. (——— prescriptions from January 1, 1990 through March 31, 2002), AERS report data suggest that the frequency of anaphylaxis associated with omeprazole is low.

This consult contains information from IMS Health National Prescription Audit Plus (on-line) and is not to be used outside of the FDA without prior clearance by IMS Health.

Reason for Request/Review: Omeprazole (Prilosec) is marketed by AstraZeneca and was approved on September 14, 1989. AstraZeneca has petitioned for an Rx to OTC switch. Because of concerns of possible allergic reactions, HFD-180 has requested a consult of allergic reactions, specifically anaphylactic reactions, associated with omeprazole use.

Relevant Product Labeling: The omeprazole labeling contains the following events in the Adverse Reactions section:
Body as a Whole: Allergic reactions, including, rarely, anaphylaxis
Cardiovascular: Chest pain, tachycardia, elevated blood pressure
Skin: Rash, and rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme; purpura and/or petechiae; skin inflammation, urticaria, angioedema, pruritus

Search Date: May 30, 2002	**Search Type(s):** AERS Literature IMS

Search Criteria: Drug Names: Omeprazole (Prilosec)
MEDDRA Terms: ODS reaction group anaphylaxis/anaphylactoid including MEDDRA terms *anaphylactoid reaction* (PT), *anaphylactic responses* (HLT)
Events captured up to April 25, 2002

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Search Results: The search identified 36 unduplicated reports of anaphylactic reactions. One domestic report was excluded because ·as later determined that the patient was allergic to the peanuts she had taken at the same time as omeprazole. The remaining 35 rts were separated by domestic and foreign. The 17 domestic cases are discussed below. The 18 foreign cases will not be ...scussed; there were no fatalities in this group.

DEMOGRAPHIC DATA FOR DOMESTIC CASES (n = 17)
AGE (YEARS): MEAN= 60, MEDIAN= 68 (RANGE 21 TO 94) (n = 14)
SEX: M (6), F (10), UNK (1)
YEAR: 1990 (1), 1991 (1), 1992 (3), 1993 (1), 1994 (1), 1997 (3), 1998 (2), 1999 (2), 2000 (3)
DOSE PER DAY: 20 MG (6), 20 MG PRN (1), 20 MG INC TO 40 MG (1), UNK (9)
ONSET TIME: MEAN = 8 DAYS, RANGE = 15 MIN to 25 DAYS (n = 6); 11 MONTHS (1), 7 YEARS (1), UNK (9)
DECHALLENGE: 7
RECHALLENGE: 2
EVENTS: ANAPHYLACTIC/ANAPHYLACTOID REACTION (15), ANAPHYLACTIC SHOCK (2)
OUTCOME: HO (8), ER VISIT (4), LIFE-THREATENING (2), UNK (3)

Representative cases:

Case# 3029016 (Mfr# 19980300573) (U.S., 1997) A 56-year-old female with no relevant medical history was placed on 20 mg of omeprazole a day as needed (indication not stated). Less than one hour after taking her first dose, she experienced flushing, rash, and syncope; she was taken to the emergency room and recovered. Three months later, the patient experienced the same events less than one hour after taking one dose of omeprazole. Her diagnosis was probable anaphylactic reaction; the events were considered life-threatening. Concomitant medications included Mevacor and ASA.

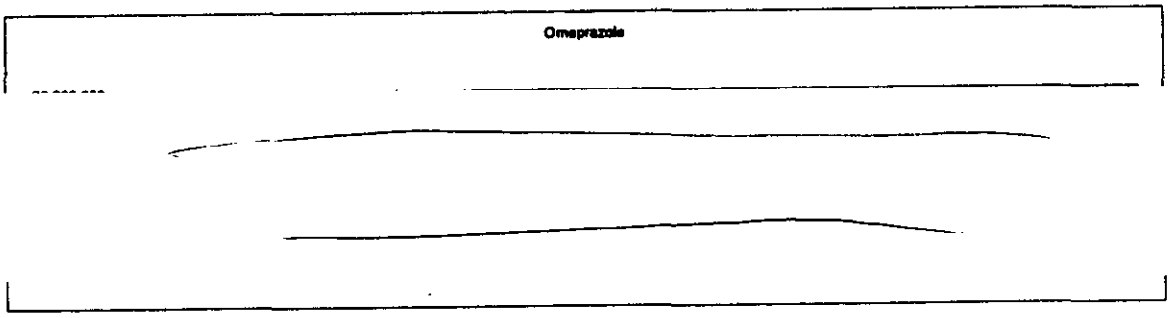
Case# 3167464 (Direct report) (U.S., 1998) A 31-year-old female developed hives, itching, difficulty swallowing, supraventricular tachycardia (SVT), and ventricular bigeminy after taking omeprazole (20 mg a day for several weeks) to treat a hiatal hernia. She was in the hospital when she developed hives, itching, and difficulty swallowing 30 minutes after her omeprazole dose; the patient was taken to telemetry where she developed SVT and ventricular bigeminy. She was treated with lidocaine. Her medical history included five months of gas and abdominal pain; no concomitant medications were reported.

TERATURE SEARCH

A search of the medical literature from 1996 to present identified three reports of anaphylactic reactions associated with omeprazole use (1, 2, 3). Note that one case (3) also was submitted as an AERS report; however, it was a foreign case and was not discussed in detail. One case involved a 54-year-old woman who developed periorbital edema, skin edema, pruritus, nausea, and vomiting 45 minutes after taking her first dose of omeprazole; she had a similar, more serious reaction 5 months later when she took her first dose of lansoprazole (1). The second case involved a 35-year-old man who developed sweating, paleness, abdominal pain, itching, dyspnea, and hypotension a few minutes after receiving an injection of omeprazole 40 mg; skin tests were positive for omeprazole and lansoprazole (2). The third case involved a 47-year-old man who developed urticaria, angioedema, hypotension, unconsciousness, and asystole after receiving 40 mg of omeprazole intravenously (he had previously developed urticaria after taking 20mg of omeprazole orally); a skin test was positive for omeprazole (3).

DRUG USE

The chart below summarizes projected total prescriptions of omeprazole dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S. from January 1, 1990 through March 31, 2002. A total of ——— prescriptions have been dispensed in the specific time period. These data come from IMS Health National Prescription Audit Plus.



* January through March

Discussion / Conclusions: Of the 17 domestic cases of anaphylactic reactions (including two cases of anaphylactic shock) associated with omeprazole use reported through AERS, there were no fatalities. The symptoms reported included skin involvement (e.g., rash, hives), edema (e.g., eyelids, throat), dizziness, flushing, and dyspnea. Three reports described cardiovascular involvement (i.e., tachycardia, supraventricular tachycardia/ventricular bigeminy, tachycardia/elevated blood pressure). Two of the reports discussed in this case series were positive rechallenges (one case is described above). For five of the reports, the report images were not available (these were submitted as periodic reports and the case narratives were not available); therefore, little is known about these cases. In addition, three reports in this case series were submitted by consumers and the quality and completeness of the data were not as good as reports received from health care practitioners. Of the three reports of anaphylaxis identified in the medical literature, two of the events occurred with the injectable dosage form of omeprazole which is not available in the U.S; there were no fatalities.

The omeprazole labeling includes anaphylaxis and other related allergic reaction events (e.g., rash, angioedema, tachycardia, elevated blood pressure). Omeprazole is used extensively in the U.S. (——— prescriptions from January 1, 1990 through March 31, 2002), AERS report data suggest that the frequency of anaphylactic reactions associated with omeprazole is low.

References:

1. Natsch S, Vinks MH, Voogt AK, et al. Anaphylactic reactions to proton-pump inhibitors. Ann Pharmacother 2000; 34: 474-6.
2. Galino PA, Borja J, Feo F, et al. Anaphylaxis to omeprazole. Ann Allergy Asthama Immunol 1999; 82: 52-4.
3. Ottervanger JP, Phaff RAS, Vermeulen EG, et al. Anaphylaxis to omeprazole. J Allery Clin Immunol 1996; 97: 1413-4.

Reviewer's Signature / Date: Ann Corken Mackey 6/10/02	**Team Leader's Signature / Date:** Lanh Green 6/10/02
Division Director Signature / Date: Julie Beitz 6/11/01	

NDA # 21-220
HFD-430 Beitz/Green/Mackey/Guinn/Birdsong/Drug
HFD-180 Korvick/Gallo-Torres/Avigon/Project Manager

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/s/

Ann Corken
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PHARMACIST

Julie Beitz
7/10/02 12:57:09 PM
DIRECTOR

ADDENDUM TO OTC MEDICAL OFFICER'S REVIEW

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

NDA #:	**21-229**
Drug name:	**Prilosec1 (omeprazole magnesium)**
Sponsor:	**AstraZeneca LP**
	Procter&Gamble Company
Pharmacologic Category:	**Proton Pump Inhibitor**
Proposed Indications:	**For Prevention of Frequent Heartburn**
Dosage Form:	**20 mg Tablet**
Route of Administration:	**Oral**
Submission dates:	**February 12, 2002**
Review date:	**July 3, 2002**
Reviewer:	**Daiva Shetty, MD**

This is an addendum to the medical officer's review dated April 16, 2002. This document addresses the of financial disclosure for the Actual Use Study 2001007.

The sponsor has submitted financial disclosure information for the investigators involved in the conduct of study 2001007. There was one principal investigator and five sub-investigators for each of the five study sites:

1. Bernard P. Schachtel, MD (coordinating investigator)
2. [redacted]
3.
4.
5.
6.

The sponsor has submitted the Form FDA 3454 certifying the absence of a financial interest by any of those investigators. There were no DSI audits conducted for the study site or data analyses.

Since there were no financial disclosures that could cast doubt on the findings, in the opinion of this reviewer, the trial was conducted in accordance with accepted ethical standards.

/S/

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

Concurrence:

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/s/

Daiva Shetty
7/3/02 12:03:37 PM
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Linda Katz
7/8/02 05:25:14 PM
MEDICAL OFFICER

JUN 1 4 2002

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **FOOD AND DRUG ADMINSTRATION**	***ODS POSTMARKETING SAFETY REVIEW***	
TO: Victor Raczkowski, M.D., Acting Director Division of Gastrointestinal & Coagulation Drug Products HFD-180	**FROM:** Ann Corken Mackey, RPh, MPH Safety Evaluator Division of Drug Risk Evaluation (DDRE) HFD-430	**ODS PID #** D020199 **Date:** June 12, 2002

DATE REQUESTED: **DATE RECEIVED:**	**REQUESTOR/Phone #:**	
DRUG (Est): Omeprazole	NDA/IND # 21-229	**SPONSOR:** AstraZeneca
DRUG NAME (Trade): Prilosec	**THERAPEUTIC CLASSIFICATION:**	

EVENT: Evaluation of Safety Profile for OTC Switch Consideration (Update)

Executive Summary: This consult was prepared in response to a request from the HFD-180 Project Manager dated April 24, 2002 to update a previous omeprazole safety review consult of August 14, 2000 (see Attachment 1) as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole from April 1, 2000 through April 25, 2002; 2851 reports were identified in the database. Both domestic and foreign reports are addressed in this document; however, the focus is on the domestic experience.

The focus of this consult is on unlabeled adverse events for omeprazole; labeled events are discussed briefly. The following unlabeled events have been reviewed: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For all of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole and no change in the types or seriousness of adverse events reported since the previous omeprazole consult were noted. A summary of these issues appears at the end of each section.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that we continue to receive reports of cancer as previously reported. A review of the literature for GI cancer diagnosis due to patient self-medication found no new significant references.

During the time period since the previous consult (April 1, 2000 through April 25, 2002), omeprazole continues to be used extensively in the U.S. (——— prescriptions from April 1, 2000 through March 31, 2002) with an average length of therapy of 6 months and AERS report data suggest that the frequency of serious adverse events associated with omeprazole continues to be low; however, with any evaluation of spontaneous reports, under-reporting must be considered (R-1, 2).

This consult contains information from IMS Health National Prescription Audit Plus (on-line) and National Disease and Therapeutic Index and ——— and is not to be used outside of the FDA without prior clearance by IMS Health and ———

Reason for Request/Review: Omeprazole (Prilosec) is indicated to treat duodenal ulcer and gastric ulcer, symptomatic GERD, erosive esophagitis, pathological hypersecretory conditions, and for maintenance of healing of erosive esophagitis. It is marketed by AstraZeneca and approved on September 14, 1989. Division HFD-180 has requested an update to a previous consult (Omeprazole Safety Review, August 2000, Attachment 1) involving a review of selected adverse events for omeprazole. AstraZeneca has petitioned for an Rx to OTC switch.

Reviewer's Signature / Date: Ann Corken Mackey 6/11/02	**Team Leader's Signature / Date: Lanh Green 6/11/02**
Division Director Signature / Date: Julie Beitz 6/12/02	**Team Leader's Signature / Date: Mary Willy 6/11/02**

Cc: NDA # 21-229
HFD-430 Beitz/Guinn /Birdsong/Green/Mackey/Willy/Chron/Drug
HFD-180 Korvick/Gallo-Torres/Project Manager

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1.0 LABELING

The current Prilosec labeling contains the following events in the ADVERSE REACTIONS section relating to the corresponding body systems discussed in this review:

Hematologic—Rare instances of pancytopenia, agranulocytosis (some fatal)

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

Gastrointestinal—Pancreatitis (some fatal)

Skin—Rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe)

Special senses—Tinnitus

Under PRECAUTIONS:

Drug Interactions—Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Pediatrics - Safety and effectiveness in pediatric patients have not been established.

Pregnancy Category C - Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Carcinogenesis - The labeling refers to studies in rats, at daily doses approximately 4 to 352 times the human dose, which produced gastric ECL cell carcinoids in a dose-related manner (incidence higher in female rats, which had higher blood levels of omeprazole). Gastric carcinoids seldom occurred in the untreated rat.

2.0 INTERNATIONAL EXPERIENCE

To date, Sweden is the only country that has granted nonprescription status to omeprazole. The MUPS dosage form of omeprazole (10 and 20 mg) was approved in April 2000 for the prevention and treatment of

heartburn. ODS has contacted the Swedish government regarding the adverse event experience since the product has received nonprescription status; they reported receipt of one report of urticaria and one report of anxiety/depressive reaction.

3.0 DRUG USE

The table below summarizes projected total prescriptions of omeprazole dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S. from April 1, 2000 through March 31, 2002. A total of [redacted] prescriptions have been filled in the specific time period.

	2000 (Apr thru Dec)	2001	2002 (Jan thru Mar)	Total
Omeprazole Prescriptions	[redacted]	[redacted]	[redacted]	[redacted]

The table below represents projected estimated proportion of omeprazole use by gender from April 1, 2000 through December 31, 2001.

Total % Use by Gender	
Female	[redacted]
Male	[redacted]
Unspecified	[redacted]
Total	[redacted]

The table below shows projected estimated proportion of omeprazole use by age category from April 1, 2000 through December 31, 2001.

Total % Use by Age Bracket (in years)	
00 to 9	[redacted]
10 to 19	[redacted]
20 to 29	[redacted]
30 to 39	[redacted]
40 to 49	[redacted]
50 to 59	[redacted]
60 to 69	[redacted]
70 to 79	[redacted]
80 to 89	[redacted]
90 to 99	[redacted]
Unspecified	[redacted]
Total	[redacted]

This information comes from IMS Health National Prescription Audit Plus (on-line) and National Disease and Therapeutic Index and is not to be used outside of the FDA without prior clearance by IMS Health.

[redacted] is one of the largest pharmacy benefit management (PBM) companies in the U.S., currently covering [redacted] patient lives and processing [redacted] prescription claims annually. FDA has on-line access to [redacted] database of paid claims for prescriptions filled in [redacted] pharmacies across the country. Patients whose claims are processed by [redacted] include those covered under various types of

insurance plans that cover prescription drugs. Demographically, these patients appear to represent all 50 states, and include substantial numbers of the elderly, children and women of childbearing age. Their representativeness of all patients receiving dispensed prescriptions in the U.S., however, is not known at this time.

A search of the , ——— database found that the average length of omeprazole therapy between June 1, 2000 and March 31, 2002 was — days. However, it cannot be determined whether these were consecutive or nonconsecutive days of therapy.

This information comes from ——— and is not to be used outside of the FDA without prior clearance by ———

4.0 ADVERSE EVENTS OVERVIEW

There are a total of 2851 adverse reaction reports of any nature for omeprazole from April 1, 2000 through April 25, 2002 in the Adverse Event Reporting System (AERS). A total of 134 reports with a death outcome will be further discussed in this document. A total of 558 reports were received from the U.S., 455 reports were received from France, 55 reports were received from Japan, 51 reports were received from the United Kingdom, and the rest were from other countries.

5.0 DEATH OUTCOME CASES

AERS was searched for reports involving omeprazole that were received through AERS from April 1, 2000 through April 25, 2002 and resulted in an outcome of death. A total of 134 reports were retrieved. From these results, a search was conducted to separate the data into domestic and foreign reports, which resulted in the identification of 17 unduplicated domestic reports; 3 reports were excluded because they were follow ups to reports discussed in the August 2000 omeprazole consult, leaving 14 reports for review. The remaining 117 foreign reports are raw numbers and do not reflect the actual number of cases (no attempt was made to review these reports). The 14 domestic cases are discussed below and under each section when applicable.

5.1 Carcinoma (n = 2)

Two cases of patients who died of cancer (i.e., throat cancer and lung cancer) were received through AERS. Both cases reported the deaths of patients who were receiving omperazole as part of their drug regimen. Very little information was provided in either of these cases; therefore, it is difficult to determine the relationship of omeprazole in the deaths of these two patients.

5.2 Drug Interactions (n = 2)

Two cases of patients who died of possible drug intereactions were received through AERS. One male patient (age not reported) received diazepam and omeprazole concomitantly during a colonoscopy and died in a car accident later that night; this is the only information that was provided. The other patient (a 47-year-old female) died of an accidental overdose of morphine, fentanyl, oxycodone, mirtazapine, and diazepam; she was taking omeprazole along with several other medications. Her medical history included dystrophy of the upper and lower extremities.

5.3 Cardiovascular events (n = 3)

Three patients died of cardiovascular events while taking omeprazole. One male patient (age not reported) expired from heart complications resulting from heart bypass surgery; he had taken two omeprazole capsules before surgery. One female patient (age not reported) died of a myocardial infarction after taking omeprazole for approximately five years (dose not stated); her medical history included congestive heart failure. A 64-

year-old male died of a myocardial infarction 24 days after starting omeprazole (20 mg/day). He also had been taking warfarin for six years because he had a stent in his leg.

5.4 Intentional suicide (n = 2)
Two cases of intentional suicide were reported through AERS. One reporter provided little information other than a 33-year-old patient (gender unknown) who committed suicide by ingesting sertraline and omeprazole. The other case involved a 44-year-old male who ingested ten medications including omeprazole; he experienced tonic-clonic seizures and cardiac arrest.

5.5 Multisystem Organ Failure (n = 2)
Two patients died of multiorgan failure while taking omeprazole. A 57-year-old female took omeprazole (40 mg/day) for an unknown duration; she experienced abdominal pain and acute renal failure with elevated liver enzymes and respiratory distress syndrome. Eventually she progressed to hepatitis, pancreatitis, disseminated intravascular coagulation and elevated white blood cell counts. Concomitant medications included glipizide, metformin, montelukast sodium, furosemide and albuterol; her medical history included adult onset diabetes, mitral valve disease, and a dilated left ventricle. The reporting physician doubted that omeprazole was the cause of her death. A 63-year-old male died of multisystem organ failure while taking omeprazole along with at least twenty concomitant medications. The patient had surgery to repair an aneurysm; he developed increased platelets and received multiple transfusions. His medical history included cirrhosis, hypertension, and diarrhea. This report was submitted by the deceased's wife and was very difficult to follow.

5.6 Miscellaneous Death Outcome Cases (n = 3)
One case involved a 28-year-old male who took one dose of omeprazole and died; concomitant medications included methadone, oxycodone, hydrocodone, and diazepam (report submitted by patient's brother and provided very little information). One case involved a 7-year-old boy with ischemic encephalopathy and "GI problems" who experienced GI bleeding, respiratory distress, disseminated intravascular coagulation and shock; he had been taking omeprazole (dose and duration unknown). An 82-year-old female experienced fever and pruritic rash eight days after starting Prevacid; she was switched to omeprazole and experienced leukopenia and thrombocytopena and died two days later.

5.7 Summary of Death Cases
Of the 14 cases described in this section, none were particularly compelling with regard to omeprazole. Most patients had underlying medical conditions making an association between omeprazole and the patient's deaths difficult to establish. There appears to be no change in the types of deaths reported since the omeprazole consult of August 2000.

6.0 PEDIATRIC EXPERIENCE

AERS was searched from April 1, 2000 through April 25, 2002 using omeprazole as suspect drug and age criteria of 0 to 16 years. The search produced 79 reports. When the search was refined to capture domestic use only, 27 reports were identified. The search was refined to identify serious (e.g., death, hospitalization, disability, life-threatening) pediatric reports from foreign sources; those 7 unduplicated cases are listed below. The 27 domestic reports were pulled for a hands-on review. A total of 11 reports were excluded for the following reasons: 2 reports were miscoded, 1 report was a follow up to a report that was discussed in the previous omeprazole consult, 1 report specified another drug (lansoprazole) as the culprit (not clear when/if patient received omeprazole), 4 reports were accidental/intentional overdoses, and 3 reports stated that omeprazole was ineffective. The remaining 16 domestic reports are discussed below.

6.1 Death (n = 1)
This case involved a 7-year-old boy with ischemic encephalopathy and "GI problems" who experienced GI bleeding, respiratory distress, disseminated intravascular coagulation and shock; he had been taking omeprazole (dose and duration unknown). Note that this case also is discussed above under the Death Outcome section.

6.2 Neurologic events (n =9)
Nine cases of neurologic events in children were received through AERS, most nonserious. One case involved a 7-year-old girl who experienced a seizure, stopped breathing, and was unresponsive ten days after her omeprazole dose was increased from 10 mg/day to 40 mg/day (total duration less than one month); she was hospitalized and recovered and continues omeprazole therapy at a lower dose. An 8-year-old girl has learning diabilities, expressive speech delay, and memory difficulties after receiving omeprazole (dose unknown) for approximately one year; concomitant medications included ondansetron and cisapride. A 6-month-old boy experienced somnolence, increased sleep time, and began eating less after taking 10 mg of omeprazole a day for 35 days; a follow up report stated that the patient also was receiving cisapride and his events were related to cisapride.

Three cases of abnormal behavior were received through AERS. A 13-year-old boy experienced behavioral changes (i.e., angry, acted out) after taking 20 mg of omeprazole a day for six days; concomitant medications included montelukast sodium, nedokromil sodium, budesonide, cromolyn sodium, and flunisolide. The reporter stated that the patient is allergic to corn, grass, and trees and could have reacted to an inactive ingredient in his medication. A 6-year-old boy experienced mood swings after taking omeprazole (dose and duration unknown); he had a history of attention deficit disorder and was receiving amphetamines. A 9-year-old boy became agitated and began fighting in school after taking 20 mg of omeprazole a day for 21 days; he also was taking methylphenidate (indication not stated). The patient began hallucinating and both drugs were discontinued; one week later methylphenidate was restarted and the patient did not have any problems.

Three cases reported as dystonia were received through AERS (two cases were reported by the same physician). One patient was a 7-month-old boy whose omeprazole was increased to 30 mg a day; he developed strange movements in his arms and legs as well as an arching of his back. A 15-month-old boy developed abnormal movements of the arms, legs, and back after taking 40 mg of omeprazole a day for an unknown duration. A 13-year-old experienced dystonia while receiving chemotherapy and ondansetron therapy (report not clear as to when omeprazole was administered); the reporter feels that the dystonia was idosyncratic because the patient had an episode at a later date when her medications were not being administered.

6.3 Miscellaneous (n = 6)
Six reports received through AERS involved miscellaneous events as described below.

Diarrhea/vomiting: A 17-month-old boy developed diarrhea and vomiting and was later discovered to have a rotavirus.
Increased uric acid levels: A 9-year-old girl experienced increased uric acid levels; a follow-up report stated that the patient had increased uric acid levels before omeprazole therapy.
Fever: A 9-month-old girl developed a fever while in a study to evaluate single dose omeprazole in the pediatric population; she was hospitalized later with a high fever/possible infection.
Muscle weakness/flu-like symptoms/abdominal pain: A 15-year-old boy experienced these symptoms while receiving 20 mg of omeprazole a day for an unknown duration; he was later determined to have mononucleosis.
Hypotonia/lethargy: A 15-month-old girl became limp and lethargic after her omeprazole dose was increased to 30 mg a day.

Cerebral hemorrhage: A 24-day-old infant suffered cerebral hemorrhage; her mother had taken omeprazole during the first 2.5 months of pregnancy and had taken ondansetron for one day during pregnancy.

6.4 Foreign Experience

A search of pediatric, foreign serious cases identified 7 unduplicated cases (note that these cases were not given a hands-on review): partial complex epilepsy (1), ventricular septal defect/cardiac murmur in a baby whose mother took omeprazole while pregnant (1), seizure (1), breath-holding spells (1), ataxia (1), drug interaction with tacrolimus (1), and seizure in a baby whose mother took omeprazole while pregnant (1).

6.5 Summary of pediatric cases

Of the 16 U.S. cases described in this section, most were nonserious and none were particularly compelling with regard to omeprazole. Most patients had underlying medical conditions making an association between omeprazole the patient's events difficult to establish. There was an increase in pediatric neurologic events since the last consult; however, the August 2000 consult looked at serious events only (e.g., death, hospitalization, disability, life-threatening). There appears to be no change in the types of pediatric adverse events reported since the omeprazole consult of August 2000.

7.0 DRUG INTERACTIONS

Omeprazole is metabolized by the cytochrome P-450 system. It is a substrate for isoenzymes 2C8, 2C18, and 2C19; an inhibitor of isoenzymes 2C8, 2C19, and 3A4; and an inducer for isoenzyme 1A2 (American College of Clinical Pharmacy [website=www.accp.com]). Therefore, omeprazole has the potential to interact with other medications also affected by these systems. The labeling states that omeprazole can prolong elimination of diazepam, warfarin, and phenytoin and that clinical reports have been received regarding interactions with cyclosporine, disulfiram, and benzodiazepines.

AERS was searched from April 1, 2000 through April 25, 2002 using omeprazole as the suspect and concomitant drug and *Drug interactions* as the MEDDRA PT. The search produced a total of 235 reports. The individual cases were reviewed for those drugs that had 5 or more reports (i.e., rofecoxib, clarithromycin, celecoxib, orlistat, aspirin, atorvastatin, citalopram, diltiazem, enoxaparin, fluconazole, and sertraline). Warfarin and cyclosporine had more than five reports, but they were excluded from this review because both are listed in the omeprazole labeling.

A hands-on review of the reports for the drugs mentioned above found no signals of possible drug interactions with omeprazole. Note that two cases of patients who died of possible drug intereactions were received through AERS during the specified time period. One male patient (age not reported) received diazepam and omeprazole concomitantly during a colonoscopy and died in a car accident later that night; this is the only information that was provided. The other patient (a 47-year-old female) died of an accidental overdose of morphine, fentanyl, oxycodone, mirtazapine, and diazepam; she was taking omeprazole along with several other medications. Her medical history included dystrophy of the upper and lower extremities. These cases also are discussed under the Death Outcome section above.

8.0 SERIOUS HEMATOLOGIC EVENTS

Pancytopenia (rare) and agranulocytosis (some fatal) are labeled events. A search of all events reported for omeprazole from April 1, 2000 through April 25, 2002 identified 16 reports of agranulocytosis and 25 reports of pancytopenia from U.S. and foreign sources (some of these may represent duplicate reporting or follow up to reports received before April 1, 2000; note that the events are not mutually exclusive). Aplastic anemia and bone marrow depression are not labeled events; the search identified 1 and 7 unduplicated reports, respectively, for these events. All cases were from foreign sources and will not be discussed in detail in this document. There appears to be no change in the types or seriousness of hematologic events reported since

the omeprazole consult of August 2000; there were no fatal cases from domestic sources. We continue to receive reports for pancytopenia and agranulocytosis even though they are labeled events.

9.0 SERIOUS LIVER EVENTS

Overt liver disease, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy are labeled events. A search of all events reported for omeprazole from April 1, 2000 through April 25, 2002 identified 57 reports of serious liver events from U.S. and foreign sources (some of these may represent duplicate reporting or follow up to reports received before April 1, 2000). A listing of the serious liver events can be found below (note that the events are not mutually exclusive). There appears to be no change in the types or seriousness of liver events reported since the omeprazole consult of August 2000; there were no fatal cases. We continue to receive reports of liver disease, liver necrosis, and hepatic failure even though they are labeled events.

Hepatic failure	11
Hepatic necrosis	2
Hepatitis cholestatic	8
Hepatitis chronic NOS	1
Hepatitis fulminant	4
Hepatitis granulomatous NOS	1
Hepatorenal failure	2
Jaundice cholestatic	1
Jaundice NOS	27

10.0 STEVENS-JOHNSON SYNDROME/TOXIC EPIDERMAL NECROLYSIS

Stevens-Johnson Syndrome (SJS) and toxic epidermal necrolysis (TEN) are labeled events. A search of all events reported for omeprazole from April 1, 2000 through April 25, 2002 identified 16 reports of SJS and 22 reports of TEN from U.S. and foreign sources (some of these may represent duplicate reporting or follow up to reports received before April 1, 2000; note that the events are not mutually exclusive). There appears to be no change in the types or seriousness of skin events reported since the omeprazole consult of August 2000; there were no fatal cases from domestic sources. We continue to receive reports of SJS and TEN even though they are labeled events.

11.0 VENTRICULAR ARRHYTHMIAS

AERS was searched for reports of ventricular arrhythmias associated with the use of omeprazole that were received by the FDA from April 1, 2000 through April 25, 2002 using the following MEDDRA terms: *Ventricular arrhythmias* (HLGT), *Electrocardiogram QT prolonged* (PT), *Electrocardiogram QT corrected interval prolonged* (PT), and *Electrocardiogram QRS complex prolonged* (PT). The search identified 23 unduplicated cases (10 domestic cases and 13 foreign cases). The 13 foreign cases are listed below. Of the 10 domestic cases, 2 cases were excluded because they were follow ups to reports submitted before April 1, 2000 and were discussed in the previous omeprazole consult and 1 case was excluded because it involved an intentional overdose (44-year-old male who experienced seizures and cardiac arrest and death). The latter case is discussed in this consult under the section Death Outcome Cases, Intentional Suicide; other than this case there were no fatal cases of ventricular arrhythmia. The remaining 7 domestic cases are discussed below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 7)

AGE (YEARS):	MEAN 54, MEDIAN 50, RANGE 48 to 66 (n = 5)
SEX:	M (4), F (2), UNK (1)
REPORTING YEAR:	1997 (1), 1998 (1), 1999 (1), 2000 (4)
REACTION ONSET:	LESS THAN 30 DAYS (2), ON/OFF FOR 2 YEARS (1), UNK (4)
DOSE PER DAY (MG):	20 MG (4), 10 MG (1), UNK (2)
DECHALLENGE POSITIVE:	1
OUTCOME:	HOSP (3)
EVENT DESCRIPTION*:	PREMATURE VENTRICULAR CONTRACTIONS (3), VENTRICULAR TACHYCARDIA (2), QT PROLONGATION (1), CHEST PAIN (2), PREMATURE ATRIAL CONTRACTIONS (1), ASYSTOLE (1), ATRIAL FIBRILLATION (1)
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE CARDIO-VASCULAR EVENTS§	4
PTS WITH HISTORY OF CARDIO-VASCULAR DISEASE#	3

* Events not mutually exclusive.
§ Concomitant medications as reported included ramipril, cisapride, and loratadine.
# Cardiovascular history as reported included cardiomyopathy, coronary artery disease, paroxysmal atrial fibrillation, PVC (controlled), and venous insufficiency.

Case of QT prolongation:
Case# 3571074 (Mfr# 20000800477) (US, 2000) A patient (gender and age not specified) experienced QT prolongation after starting omeprazole therapy (dose and duration not specified). The patient had had a normal EKG before starting omeprazole therapy. Very little information was provided by the physician.

In addition to the domestic cases that were individually reviewed, there were 13 foreign cases of cardiac events in AERS. These events included the following: cardiac arrest (7 cases), ventricular fibrillation/ventricular tachycardia (2 cases), syncope/hypotension (1 case), QT prolongation (1 case), myocardial infarction (1 case), and ventricular extrasystole/supraventricular extrasystole (1 case). These cases were not given a hands-on review.

11.1 Summary of ventricular arrhythmia cases

There are no ventricular arrhythmia events listed in the labeling for omeprazole. Of the cases described in this consult, three patients were taking concomitant medications with known cardiac adverse event profiles (e.g., cisapride) and four patients had a history of cardiovascular disease. One report was submitted by an attorney on behalf of a patient who had taken troglitazone and developed liver failure and PVCs. Because of concomitant medications, confounding medical history, and little information provided in several of the cases, it is difficult to make a determination about omeprazole and serious cardiac adverse events, especially ventricular arrhythmias. The types and seriousness of ventricular arrhythmic events have not changed since the omeprazole consult of August 2000.

12.0 PANCREATITIS

Pancreatitis (some fatal) is a labeled event. A search of all events reported for omeprazole from April 1, 2000 through April 25, 2002 identified 17 reports of pancreatic adverse events (some of these may represent duplicate reporting or follow up to reports received before April, 1, 2000). A listing of the pancreatic events

can be found below; this list includes U.S. plus foreign reports (note that the events are not mutually exclusive). There appears to be no change in the types or seriousness of pancreatic events reported since the omeprazole consult of August 2000; there were no fatal cases from domestic sources. We continue to receive reports of pancreatitis even though it is a labeled event.

Pancreatitis Acute	5
Pancreatitis Haemorrhagic	2
Pancreatitis Necrotising	1
Pancreatitis Nos	9

13.0 OPHTHALMOLOGIC EVENTS

This section also responds to a consult dated April 16, 2002 from HFD-180 for a search of the AERS database for cases of visual disturbances (including blindness) associated with the use of omeprazole. The purpose of that request was to provide documentation for the addition of "blurred vision" and "eye irritation" to the Adverse Reactions section of the omeprazole labeling, as requested by the manufacturer.

Note that four previous consults have been completed at HFD-180's request regarding this issue. The case inclusion date for the most recent consult was March 31, 2000 (Attachment 1). The reader is encouraged to review the previous document.

To update the previous consults, AERS was searched using omeprazole as suspect drug and *Eye Disorders* as the MedDRA System Organ Class (SOC) term. This search produced a total of 103 reports. A listing of the eye events with 4 or more cases is presented below (some of these numbers may represent duplicate reporting; note that the events are not mutually exclusive).

In order to evaluate the most severe outcome of an ophthalmic event, a second search using omeprazole as suspect drug and *Blindness* as the MedDRA HLT was performed from April 1, 2000 to April 25, 2002. This search produced a total of two reports (one domestic case and one foreign case). The foreign case will not be discussed. The domestic case involved a 45-year-old female who had periodic spells of vision loss for about five minutes each. The patient is diabetic (uncontrolled per glucose values) and takes glipizide and metformin when "she can afford" them. Concomitant medications included simvastatin and omeprazole; she had an infected right foot. This report was from a consumer and provided very little information.

SOC EYE DISORDERS: EVENTS WITH 4 OR MORE CASES (U.S. PLUS FOREIGN)

Conjunctivitis NOS	4
Diplopia	7
Dry Eye NOS	10
Eye Disorder NOS	6
Eye Irritation	4
Eye Pain	5
Vision Abnormal NOS	6
Vision Blurred	22
Visual Disturbance NOS	15

13.1 Summary of Ophthalmologic Events

This information updates 4 previous consults regarding omeprazole and ophthalmic events. ODS was asked specifically about AERS cases of blurred vision and eye irritation, as these relate to a manufacturer's request for labeling change. In addition, we looked at one case of blindness; this case was very confounded. From

the recent printout of all visual disturbances associated with omeprazole use, there are a total of 22 reports of blurred vision. There are a total of 4 reports of eye irritation in AERS. Note that eye irritation also could include eye pain (5 reports), dry eye (10 reports), conjunctivitis (4 reports), as well as other terms. It appears that we continue to receive AERS reports of blurred vision, eye irritation, and other ophthalmologic events associated with the use of omeprazole. However, it is difficult to establish a clear relationship between omeprazole use and these events, particularly because of the extensive use of omeprazole in the U.S. ODS does not object to the inclusion of these events in the labeling as requested by the sponsor.

14.0 HEARING DISORDERS

AERS was searched for reports of hearing disorders associated with the use of omeprazole that were received by FDA from April 1, 2000 through April 25, 2002. Terms used for the search were *Hearing Disorders* (HLGT), and *Inner Ear & VIIIth Cranial Nerve Disorders* (HLGT). A total of 14 unduplicated domestic reports and 7 unduplicated foreign reports were retrieved. The foreign reports are discussed below. The 14 domestic cases are described below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 14)

AGE (YEARS):	MEAN 56, MEDIAN 58, RANGE 41 to 73 (n = 10)
SEX:	M (6), F (7), UNK (1)
REPORTING YEAR:	1999 (5), 2000 (9)
REACTION ONSET (DAYS):	2 TO 30 DAYS (5), 1.5 TO 2 YEARS (3), UNK (6)
DOSE PER DAY (MG):	20 MG (7), 10 mg (1), 20 TO 40 mg (1), UNK (5)
DECHALLENGE POSITIVE:	5
RECHALLENGE POSITIVE:	1
OUTCOME:	HOSP (1)
EVENT DESCRIPTION:	SUDDEN DEAFNESS (1), HEARING WORSENED (3), VERTIGO (6), TINNITUS (2), "ROARING IN EARS" (1), MOTION SICKNESS (1)
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEARING DISORDERS*	6

* Concomitant medications included gentamycin, albuterol, lisinopril, atorvastatin, and diazepam.

Case of sudden deafness (other cases not well described and less compelling):
Case# 3772861 (Mfr# 2002UW02804) (2000) A 62-year-old female experienced sudden deafness requiring hospitalization while taking omeprazole (strength and duration of use not reported). Her medical history included hypertension, Wolff-Parkinson-White syndrome, gastric ulcers, and eczema. She had received betamethasone and gentamicin at some point (timeframe not clear). This was a consumer report and very little information was provided.

In addition to the domestic cases that were individually reviewed there were 7 foreign cases. A hands-on review of the foreign cases was not performed. The following counts of hearing disorders were noted: vertigo (5), tinnitus (1), deafness (1).

14.1 Summary of hearing disorder cases

Tinnitis is a labeled event. This section describes 14 domestic cases of hearing disorders possibly associated with the use of omeprazole. Of the cases described above, 6 patients were taking concomitant medications with labeled hearing events, one patient's vertigo was reported during an ocean cruise, one patient was found

to have an inner ear infection, and one patient was later found to have fluid on the ears. Nine of these reports were submitted by consumers, and were lacking in relevant information (e.g., concomitant medications, relevant history, description of event). The poor quality of these reports makes it difficult to assess causality or severity. Overall, there have been no changes in the types or seriousness of hearing disorders reported since the August 2000 omeprazole consult.

15.0 CANCER DATA AND DELAYS IN DIAGNOSIS IN THE LITERATURE

Two previous memoranda have been completed, one dated July 30, 1999 and a second from August 14, 2000 (Attachment 1), summarizing medical literature reviews and worldwide post-marketing reports for tumors associated with proton pump inhibitors including omeprazole. The early medical literature review included a discussion of animal studies that showed generalized hyperplasia of the gastric mucosa, but no human studies that proved carcinogenesis. The second review identified a few possible cases of omeprazole-related cancers (one patient with an argyrophil-positive carcinoid tumor and three patients with adenocarcinoma).

An updated review of the medical literature was obtained on May 3, 2002 to look for case reports of cancer associated with ompeprazole, rabeprazole, pantoprazole or lansoprazole. A related issue, diagnostic delays, was also included in the search. The following databases were searched: PubMed, Embase, Derwent-Drug-File, BIOSIS, International-Pharmaceutical-Abstracts, Life-Sciences, and Cancerlit. The search identified 122 possible references. One of the references summarized the report of a case of gastric carcinoid developing in a 56 year-old woman who received four years of 40 mg omeprazole daily (R-3). No study was identified that studied substantial number of patients for extended (more than 10 years) of time. One group of investigators (R-4) describe their patients as having a "very long (up to 10 years)" treatment duration (but only 27 patients (44%) were treated more than 10 years).

The medical literature search also identified: 1) a number of papers that discuss the issue of proton pump inhibitor-related cancer risk providing a review of a variety of studies exploring risk factors (R-5-7)'and 2) a study that concluded antisecretory therapy prior to gastroscopy might delay the detection of gastrointestinal malignancies, although the findings are not generalizable to the U.S. since it was carried out in England where the author reported many patients experience an extended wait for diagnostic testing (up to 10 weeks) (R-8).

15.1 CANCER REPORTS IN AERS

Two updated AERS searches (data from 3/31/2000 to 4/26/2002) were performed relating to cases of cancer. The first search included the SOC Neoplasms benign and malignant (including cysts and polyps). This broad search revealed a total of 98 cases. Twenty-seven cases were domestic, 38 were foreign and in 33 reporter country was unknown. The only neoplasm events of any nature among the 98 cases which had counts of 5 or more (some may be duplicates) were gastric polyps (24), oesphageal carcinoma nos (7 reports) and polyps nos (5 reports). Neoplasm events with at least 3 counts were: adenocarcinoma nos, Barrett's oesophagus, carcinoid tumour of the stomach, carcinoma nos, cyst nos, gastric cancer nos, myeloid leukaemia nos, and renal cell carcinoma stage unspecified.

In the previous analysis a second search utilized the HLGT Gastrointestinal neoplasms malignant and unspecified to study duration of use and cancer onset. In this update a similar search was completed and revealed 42 cases (domestic and foreign); very little information was provided on duration making it difficult to assess how long the patients used the drug. Given the small number of cases a repeat analysis was not completed.

16.0 DISCUSSION/CONCLUSION

The focus of this consult is on unlabeled adverse events for omeprazole; labeled events are discussed briefly. The following events have been reviewed: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, ventricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For all of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole and no change in the types or seriousness of adverse events reported since the previous omeprazole consult were noted. A summary of these issues appears at the end of each section.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that we continue to receive reports of cancer as previously noted. A review of the literature for reports of delays in GI cancer diagnosis due to patient self-medication found no new significant references.

During the time period since the previous consult (April 1, 2000 through April 25, 2002), omeprazole continues to be used extensively in the U.S. (prescriptions from April 1, 2000 through March 31, 2002) with an average length of therapy of 6 months. AERS report data suggest that the frequency of serious adverse events associated with omeprazole continues to be low; however, with any evaluation of spontaneous reports, under-reporting must be considered (R-1, 2).

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ATTACHMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE **FOOD AND DRUG ADMINSTRATION**	Attachment 1 ***OPDRA POSTMARKETING SAFETY REVIEW***	
TO: Lilia Talarico, M.D., Director Division of Gastrointestinal and Coagulation Drug Products HFD-180	**FROM:** Ann Corken, RPh, MPH, Safety Evaluator Mary Willy, PhD, Epidemiologist Ron Wassel, Pharm.D, Safety Evaluator Division of Drug Risk Evaluation I I (DDREII) HFD-440	**OPDRA PID #** D000223 Date sent: 8/14/00

DATE REQUESTED:
March 15, 2000

NDA #21-229 ***SPONSOR: Merck***

DRUG:
OMEPRAZOLE (PRILOSEC)

EVENT:
EVALUATION OF SAFETY PROFILE FOR OTC SWITCH CONSIDERATION

Executive Summary: This consult was prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review selected adverse events for omeprazole as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole up to March 31, 2000; 10,005 reports were identified in the database. Both domestic and foreign experience is addressed in this document, however, the focus is on the domestic experience.

The following issues have been reviewed in this consult: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For many of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole; many patients had underlying conditions or were taking concomitant medications which could have contributed to the events. Summary of these issues appears at the end of each section. The most compelling issue reviewed was serious liver events, which were temporally related to omeprazole use and included serious outcomes such as liver transplants, deaths, and encephalopathy. Serious liver events are included in the current labeling for omeprazole. The pediatric cases reviewed tended to mirror events seen in adults; these typically were not healthy children prior to omeprazole use.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that there was a trend for larger numbers of reports with a longer duration of omeprazole use, however, conclusions cannot be made because the data was derived from small numbers of spontaneous reports in the system. A review of the literature for omeprazole-related cancer revealed that the studies had limited numbers of patients exposed for short time periods with limited follow-ups. A review of the studies and case reports in the literature for delays in GI cancer diagnosis due to patient self-medication revealed that both prescription and OTC use of antacid drugs may delay diagnosis; additional studies are needed. Data regarding congenital anomalies will be addressed in a separate document.

Given the number of years that omeprazole has been on the market (11 years) and its extensive use (——— ' prescriptions), AERS report data suggest that the frequency of serious adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, underreporting must be considered.

Reason for Request/Review:
Omeprazole (Prilosec) is indicated to treat duodenal ulcer and gastric ulcer, symptomatic GERD, erosive esophagitis, pathological hypersecretory conditions, and for maintanence of healing of erosive esophagitis. It is marketed by Astra Merck and was approved on September 14, 1989. Division HFD-180 has requested a review of selected adverse events for omeprazole because Astra Merck has petitioned for an Rx to OTC switch.

Reviewers' Signatures / Date:	Team Leader's Signature / Date:
Ann Corken, RPh, M.P.H. Mary Willy, Ph.D. Ron Wassel, Pharm.D.	Toni Piazza-Hepp, Pharm.D.
Division Director Signature / Date: Evelyn Rodriguez, M.D., M.P.H.	
Cc: NDA # 21-229 HFD-180 Division File/Div Dir / MO / SMO / Project Manager HFD-560 Division File/Div Dir / MO / SMO / Project Manager HFD-440 Rodriguez/Willy/Corken/Wassel/Piazza-Hepp/Chron/Drug HFD-400 Honig	

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1.0 LABELING

The current Prilosec labeling contains the following events in the ADVERSE REACTIONS section relating to the corresponding body systems discussed in this review:

Hematologic—Rare instances of pancytopenia, agranulocytosis (some fatal)

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

Gastrointestinal—Pancreatitis (some fatal)

Skin—Rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe)

Special senses—Tinnitus

Under PRECAUTIONS:

Drug Interactions—Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Pediatrics - Safety and effectiveness in pediatric patients have not been established.

Pregnancy Category C - Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Carcinogenesis - The labeling refers to studies in rats, at daily doses approximately 4 to 352 times the human dose, which produced gastric ECL cell carcinoids in a dose-related manner (incidence higher in female rats, which had higher blood levels of omeprazole). Gastric carcinoids seldom occurred in the untreated rat.

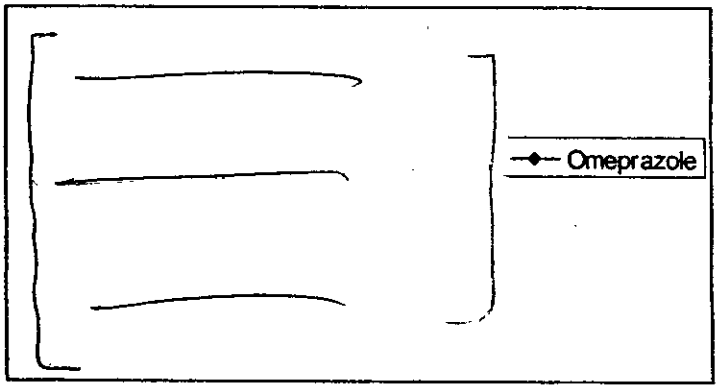
2.0 INTERNATIONAL EXPERIENCE

To date, Sweden is the only country that has granted nonprescription status to omeprazole. The MUPS dosage form (10 and 20 mg) of omeprazole was approved in April 2000 for the prevention and treatment of heartburn. Since the switch was recent, there are no data regarding nonprescription use in Sweden.

3.0 DRUG USE

The chart below summarizes projected total prescriptions of omeprazole dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S. from January 1, 1990 through March 31, 2000. A total of [redacted] prescriptions have been filled in the specified time period.

*Jan-Mar



The table below represents projected estimated proportion of omeprazole use by gender from January 1, 1989 through March 31, 2000.

Total % Use by Gender	
Female	[redacted]
Male	
Unspec	
Total	100%

The table below shows projected estimated proportion of omeprazole use by age category from January 1, 1989 through March 31, 2000.

Total% Use by Age Bracket (in years)	
00 to 10	
11 to 20	
21 to 30	
31 to 40	
41 to 50	
51 to 60	
61 to 70	
71 to 80	
81 to 90	
91 to 100	
101-110	
Unspec	
Total	100%

APPEARS THIS WAY
ON ORIGINAL

This information is from IMS HEALTH National Prescription Audit Plus (NPA)™ and National Disease and Therapeutic Index (NDTI)™ and is not to be used outside of the FDA without prior clearance by IMS Health.

4.0 ADVERSE EVENTS OVERVIEW

There are a total of 10,005 adverse reaction reports of any nature for omeprazole from time of marketing through March 31, 2000 in the Adverse Event Reporting System (AERS). A total of 579 reports with a death outcome will be further discussed in this document. More than half (5431) of the reports were received from the U.S.; 533 of the reports were received from France, 298 of the reports were received from the United Kingdom, 203 of the reports were received from Germany, and 180 of the reports were received from Japan. Attachment A is a listing of MEDDRA Preferred terms (PT) by decreasing order of frequency where there were 10 or more cases per event in AERS. Since these are raw figures from AERS, some of the numbers may represent duplicates.

5.0 DEATH OUTCOME CASES

AERS was searched for reports involving omeprazole that were received by the FDA up through and including March 31, 2000 and resulted in an outcome of death. A total of 579 reports were retrieved. From these results, a search was conducted to separate the data into domestic and foreign reports, which resulted in the identification of 184 domestic reports. The remaining 395 foreign reports is a raw number and does not reflect the actual number of cases (no attempt was made to review these reports). Reviewing these 184 domestic reports identified 98 unduplicated cases. Of the 98 cases, 52 were excluded from further review for the following reasons: 3 cases that were actually foreign reports, 3 cases that were incorrectly entered into AERS as having a death outcome, 1 case in which the adverse event that led to the patient's death (bone marrow depression) was present prior to omeprazole therapy, and the remainder in which the patient's death was not related to the use of omeprazole but rather their underlying disease such as sepsis or carcinoma. The remaining 46 cases were analyzed for cause of death and are discussed below.

5.1 Gastric carcinoma ($n = 3$)

Three cases, although probably not omeprazole–related deaths, are of interest to report here in that they involved the use of omeprazole for stomach pain in which the patients eventually died due to gastric carcinoma. Two of these cases (one unknown demographics; one 46-year-old male) involved short–term omeprazole use with no relief of pain and were eventually diagnosed with the malignancy. One case (unknown demographics) was described as the "patient died from stomach cancer after two and a half years of therapy with omeprazole."

Another case involved an 80-year-old male who took omeprazole 20 mg daily for seven years for the treatment of gastroesophageal reflux disease. The patient was eventually diagnosed with "abdominal carcinomatosis" with a biopsy revealing "adeno-carcinoid carcinoma." The patient had a history of pancreatic cancer treated with four courses of chemotherapy and had documented "carcinomatosis of the peritoneal cavity." Two years after the original diagnosis of abdominal carcinomatosis, biopsies of the gastric body and antrum revealed "mild to moderate chronic gastritis with no malignancies, no metastatic disease, no intestinal metaplasia, no helicobacter and no mention of enterochromaffin cell hyperplasia or carcinoid." The reporter indicated the patient died from "probable poorly differentiated neuroendocrine carcinoma of unknown primary."

5.2 Complications of pregnancy (n = 4)

There were four cases involving the death of a fetus or infant in which the women took omeprazole during their pregnancy. Two of the cases were stillbirths, one case involved a child born with hydranencephaly who died on day 1, and one case of a child born with a hypoplastic heart who eventually died on day 74 following numerous open heart procedures.

5.3 Drug interactions (n = 9)

There were nine cases in which the death outcome may have been due to a drug interaction. Each of the offending drugs is involved in the cytochrome P-450 metabolic pathway. Six of the cases reported the cause of death as cardiac arrest or sudden death. In these six cases, four involved cisapride, one involved amitriptyline, and one involved nicardipine. The other three cases in which the cause of death was not reported involved one case each of the use of omeprazole with fluconazole, clarithromycin, and cisapride.

5.4 Hepatic failure (n = 8)

Demographic data

AGE (years) (n = 7):	Range—48 to 83 years; Median—66 years; Mean—66
SEX:	Female—4; Male—4
REPORTING YEAR:	1990—2; 1992, 1996, 1997—1 each; Unknown—3
REACTION ONSET (DAYS) (n=5):	Range—7 to 150 (approx.) days; Median—13 days; Mean—48 days (approx.)
DOSE PER DAY (n = 7):	20 mg—6; 40 mg—1

In six of the eight cases there were possible confounding factors including a history of alcohol abuse (two cases), a history of liver disease (two cases), and concomitant drug therapy that has been associated with liver dysfunction (one case with pravastatin and one case with quinapril).

Representative Case of Hepatic Failure Death

Case# 5336663 (Mfr.# 19951100203) A 62-year-old male with a history of intermittent epigastric and right upper quadrant pain associated with reflux symptoms unsuccessfully treated with ranitidine, erosive esophagitis, hypertension, and coronary artery disease was placed on therapy with omeprazole 20 mg daily. Other medication, which the patient had been taking for over one year, included atenolol, diltiazem, and aspirin. Seventeen days after starting omeprazole, the patient was hospitalized with a four day history of worsening epigastric pain, anorexia, nausea and vomiting, and one day of weakness and dizziness. The patient denied any history of hepatitis, blood transfusions, toxin exposures, alcohol or acetaminophen use. He was alert with a mild slowing of mentation and a slight flapping tremor. By the next morning he was obtunded. His ammonia had reached 238 micromol/L and his asterixis was much more marked. He was transferred to another hospital for a possible liver transplant, but no liver donor was available. Hepatitis serologies were all negative. His hospital course was complicated by respiratory failure, oliguric renal failure, and seizures and he died five days after initial presentation. Autopsy revealed severe hepatic necrosis and special stains for other causes were negative. This was reported in the published article Jochem V, Kirkpatrick R, Greenson J, et al. Fulminant hepatic failure related to omeprazole. Am J Gastroenterology 1992; 87: 523-5.

5.5 Pancytopenia / Bone marrow depression (n = 3)

Demographic data

AGE (years):	Range—60 to 85 years; Median—66 years; Mean—70.3 SEX: Female—1; Male—2
REPORTING YEAR:	1990—1; 1993—1; Unknown—1
REACTION ONSET (DAYS):	Range—6 to 11 (approx.) days; Median—7 days; Mean—8 days (approx.)
DOSE PER DAY:	20 mg—1; 40 mg—1; 80 mg—1

Two of the cases had potentially confounding drug therapy with known adverse hematologic effects including the use of nortriptyline and ranitidine in one case, and multiple drug therapy with several antibiotics in the other.

Representative Case of Bone Marrow Depression Death

Case# 5512622 (Mfr.# 19961100176) An 85-year-old male with upper gastrointestinal bleeding secondary to gastric ulcer disease with gastritis and positive Helicobacter pylori was placed on therapy with omeprazole 20 mg twice a day along with clarithromycin 500 mg three times a day and metronidazole 500 mg three times a day. Six days later the patient was admitted to the hospital because of the following reported lab values: WBC 900 (25% seg), platelets 26,000, bilirubin 7.7, AST 6 times normal, ALT 2.5 times normal, and alkaline phosphatase 3 times normal. The patient's bone marrow showed almost complete bone marrow failure and subsequently he died secondary to severe sepsis.

5.6 Congestive heart failure (n = 3)

Demographic data

AGE (years) (n = 2):	54 and 56
SEX:	Female—2; Male—1
REPORTING YEAR:	1990—1; 1994—1; Unknown—1
REACTION ONSET:	6 days; 3 months; 4 years
DOSE PER DAY:	20 mg—1; 40 mg—1; 120 mg—1

In two of the cases the patients had a history of CHF prior to omeprazole therapy, but developed worsening heart failure and eventually died. In the case in which the patient had been taking omeprazole for four years, he had a severe myocardial infarction complicated by several cardiac arrests, which led to poor myocardial function and eventual death from heart failure. Whether omeprazole contributed to diminished cardiac function in any of these cases is unknown.

5.6 Miscellaneous Death Outcome Cases
There was one case of **toxic epidermal necrolysis** in a 77-year-old male after 15 days of omeprazole therapy 20 mg daily.

In another case, a male of unknown age developed an ileus and subsequent **pancreatitis** within one week after initiation of omeprazole therapy. Concomitant therapy included Augmentin, furosemide and an unspecified steroid for what was believed to be an immune-related thrombocytopenia. He was hospitalized, underwent surgery and died post-operatively.

There were two cases of deaths following **gastrointestinal hemorrhage** in patients of unknown age and gender. In one case omeprazole was given after intravenous cimetidine was used to treat the hemorrhage, but the patient subsequently experienced another hemorrhage and died. In the other case it is unclear whether the patient bled while on omeprazole or was being treated for the bleeding with omeprazole and eventually died.

An 87-year-old male treated with omeprazole 20 mg daily for approximately 8 months died from a "gastric outlet obstruction and prolonged complications."

One patient committed **suicide** soon after starting omeprazole.

A case of **lymphoma** occurred in a male patient treated with omeprazole 20 mg daily for approximately 2 years for the treatment of reflux esophagitis.

There were eight poorly documented cases that were generally reported as death occurring while taking omeprazole or shortly after initiating omeprazole therapy. Three of these cases may have been related to a cardiac arrest or arrhythmia, one case was reported as possibly related to the liver or the kidneys, and one case was noted to have a pain in the leg with subsequent chest pain prior to the patient's death.

5.7 Summary of Death Cases

Of the 46 cases that were reviewed, the most compelling cases had causes of death due to hepatic failure and bone marrow depression. The product labeling for omeprazole includes hepatic failure, pancytopenia/agranulocytosis, toxic epidermal necrolysis and pancreatitis as events with reports of fatalities. Deaths attributed to drug interactions and complications of pregnancy are also noteworthy. The one case of suicide may be of note in that depression is listed in the product labeling. It is difficult to make any kind of determination in the cases of congestive heart failure, gastrointestinal hemorrhage, gastric outlet obstruction, and lymphoma.

In the drug interaction section, mention is made that patients should be monitored to determine the necessity of adjusting the dosage of drugs metabolized by the cytochrome P-450 system when taken concurrently with omeprazole, although few drugs are given as examples (none of which are those that are mentioned above). In regard to pregnancy, the product labeling lists omeprazole as Pregnancy Category C and discusses sporadic reports of congenital abnormalities in humans and embryo/fetal toxicity in animals.

6.0 PEDIATRIC EXPERIENCE

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and age criteria of 0 to 16 years. The search produced 182 reports. These 182 cases were separated into serious (i.e., hospitalization, death, life threatening, disability) and nonserious outcomes; the cases with serious outcomes were separated into domestic and foreign and then checked for duplicates. Among these were 19 cases of congenital anomalies; an assessment of these cases along with other available epidemiologic data on this topic will be provided in a separate document. There were 20 other domestic pediatric cases and 28 foreign cases of a serious nature for review.

6.1 Deaths (n = 8)

There were a total of eight reports of deaths in children receiving omeprazole; seven of these reports were from foreign sources. Three patients died of cardiac arrhythmias; all three patients also were receiving cisapride concomitantly. Two patients died of hematologic events (thrombocytopenia and aplastic anemia); both patients had other serious medical conditions and were taking numerous concomitant medications. Two patients with end-stage renal failure received omeprazole; both patients received other medications that were considered suspect by the reporters. One patient experienced sepsis and died of cardiac arrest. One of the patients described above had received the IV form of omeprazole. These reports also are described below under their respective categories.

6.2 Carcinoma or neoplasms (n = 3)
U.S. experience- There were two cases. A 16-year-old boy developed a gastrin-producing chromafin-cell hyperplasia after taking 40 mg of omeprazole a day for an unknown duration; no other information was available. A 14-year-old boy was thought to have developed gastric carcinoma after taking 20 mg of omeprazole a day for an unknown duration; subsequent tests did not indicate carcinoma.

Foreign experience-One case of a testicular cyst was received through AERS.

6.3 Cardiac events (n = 5)
U.S. experience- A single case was identified of a 7-year-old boy who developed ventricular fibrillation and torsades de pointes and died after receiving 40 mg of omeprazole a day for 2.5 years; he had a history of congenital heart disease and was receiving numerous concomitant medications including cisapride.

Foreign experience-There were two cases of tachycardia, one case of QT prolongation/ asystole/cardiac arrest leading to death; both patients were receiving cisapride. There was one case of cardiac arrest leading to death.

6.4 Gastrointestinal events (n = 6)
U.S. experience-No cases of serious gastrointestinal events were received through AERS.

Foreign experience-There was one case of rectal hemorrhage, one case of severe epigastric pain and nausea, one case of epigastric pain and colic, one case of severe bloating and cramping, one case of hematemesis, and one case of GI hemorrhage reported through AERS; all patients had to be hospitalized because of the event.

6.5 Hematologic events (n = 5)
U.S. experience-There were two cases. A 15-year-old girl experienced thrombocytopenia (platelet count = 80,000) after taking 20 mg of omeprazole a day for two to three weeks; the event abated when omeprazole was discontinued. Her medical history included dyspepsia and Evans Syndrome; concomitant medication included prednisone. A 13-year-old girl experienced anemia, hematuria, lupus-like syndrome, and possible autoimmune syndrome after taking 20 mg of omeprazole a day for approximately three months; her symptoms worsened when omeprazole was replaced with ranitidine. Omeprazole therapy was reinitiated; the patient's outcome was not reported.

Foreign experience-There was one case of thrombocytopenia/leukocytosis, one case of thrombocytopenia, and one case of thrombocytopenia/aplastic anemia received through AERS. Two of these patients died.

Hepatic disorders (n = 2)
U.S. experience-A 15-year-old boy developed hepatitis after taking 20 mg of omeprazole a day for two months; the event abated when omeprazole was discontinued. The report provided very little information regarding the patient's medical history and concomitant medications.

Foreign experience-One case of increased liver enzymes was received through AERS.

6.6 Neurological events (n = 9)
U.S. experience-There were six cases. A 2-year-old boy developed ataxia, gait abnormalities, and coordination problems after taking 7 to 9 mg of omeprazole a day (duration unknown); the events resolved when omeprazole was discontinued and reappeared when omeprazole was reintroduced. Concomitant medications included cisapride, Benadryl, Intal, and Atrovent. The dose was titrated down and the patient continued on therapy without incident. A 12-year-old girl developed breakthrough seizures when omeprazole was added to her medication regimen that included phenytoin; her phenytoin levels were stable, but began fluctuating when omeprazole was introduced. The patient had a history of seizures, encephalopathy, attention-deficit disorder, possible hypothyroidism, and porphyria. She continued on omeprazole; her outcome was not reported. A 3-year-old girl with brain damage developed multiple seizures after taking 20 mg of omeprazole a day (duration not specified); concomitant medication included Depakote. The outcome was not specified; very little information was provided. A 10-year-old boy experienced a change in carbamazepine levels after taking 10 mg of omeprazole a day (duration unknown); his outcome was not reported. He had a history of seizures and was physically disabled; concomitant medications included carbamazepine, terbinafine, and diazepam. A 5-year-old girl experienced seizures (both focal and general) after receiving 20 mg of omeprazole a day (duration unknown); an EEG indicated a diagnosis of benign rolandic epilepsy. Concomitant medication included amoxicillin and Biaxin. Omeprazole was discontinued; the reporter stated that a lowered seizure threshold triggered seizures which is consistent with benign rolandic epilepsy. A 13-year-old girl experienced one seizure among other medical events (consumer report).

Foreign experience-One patient experienced an exacerbation of her movement disorder, one patient experienced extreme vertigo, and another patient experienced an increase in seizure activity.

6.7 Pancreatic events (n = 5)
U.S. experience-There were three cases. An 8-year-old boy with leukemia developed pancreatitis after taking 20 mg of omeprazole a day for six months; concomitant medications and outcome were not reported. A 3-year-old boy developed pancreatitis after taking 20 mg of cisapride a day (duration unknown); his outcome was not reported. His medical history included cerebral palsy, convulsions, and esophageal reflux; concomitant medications included cisapride, valproic acid, and multivitamins. A 14-year-old girl experienced elevated amylase and lipase after taking 40 mg of omeprazole a day for 3 days; she continued to take omeprazole and was diagnosed with pancreatitis 12 days later. The event was beginning to resolve when omeprazole was discontinued. Concomitant medications included acyclovir, Mag-Ox, prednisone, Procardia, Ativan, Zantac, and Lo/Ovral; her medical history included reflux esophagitis and aplastic anemia for which she was receiving a bone marrow transplant at the time of the report.

Foreign experience: There were two cases of pancreatitis received through AERS. One patient was receiving IV omeprazole; both patients had extensive medical histories and were taking numerous concomitant medications.

6.8 Renal events (n = 5).
U.S. experience-There were two cases. A 12-year-old boy developed an increase in creatinine (from 0.5 to 1.7) and an increase in blood urea nitrogen (BUN) (to 24 [baseline not reported]) after taking 20 mg of omeprazole a day for one week; the patient had Sanfilippi's syndrome, diabetes insipidus, hyponatremia, and acute urinary retention. Omeprazole therapy continued and his BUN and creatinine returned to normal. A 10-month-old boy developed nephrotic syndrome after taking 20 mg of omeprazole a day for one month; little information was provided other than the history of cystic fibrosis.

Foreign experience-One case of a patient with acute renal failure with hematuria and interstitial nephritis was received through AERS. Two patients in end stage renal failure received omeprazole and eventually died; both both patients received concomitant medications that were considered suspect by the reporter. One of those patients was receiving IV omeprazole.

6.9 Special senses (n = 4)
U.S. experience- A 6-year-old boy developed tinnitus and hearing loss soon after taking 5 mg of omeprazole a day to treat a stomach ulcer; eight months later the patient underwent an audiogram which revealed a significant drop in the high frequency range.

Foreign experience-There were two cases of blindness (one patient had optic neuritis and the other patient was receiving IV omeprazole) and one case of blurred vision received through AERS. The patient receiving IV omeprazole died (note that this case has been discussed under renal events as well).

6.10 Miscellaneous pediatric events (n = 5)
U.S. experience-There were two cases. A 12-year-old girl experienced diarrhea, rash, headache, backache, stomachache, tightening of the throat, and wheezing after taking 20 mg of omeprazole a day for 16 days. The patient had developed stridor and "noisy breathing" following an influenza-like illness. Omeprazole was stopped and the patient was reported as doing very well. Her medical history included GERD and depressive disorder; concomitant medications were not reported. A 7-year-old boy experienced metabolic acidosis after receiving 20 mg of omeprazole a day (duration unknown); his outcome was not reported. His medical history included partial epilepsy and changes in mental status; concomitant medication included phenytoin.

Foreign experience-There was one case of a polymyositis-like reaction, one case of a dermatomyositis-type reaction, and one case of angioedema and oral thrush reported through AERS.

6.11 Summary of pediatric events
The omeprazole labeling states that safety and effectiveness in children has not been established. The use of omeprazole in children represents less that 3% of total use. None of the pediatric reports received through AERS were particularly compelling. In general, most the pediatric patients described in this section had underlying conditions or were receiving concomitant medications making it difficult relate their outcome to omeprazole use. Further, the types of notable events were consistent with those of concern in adults (i.e. pancreatitis, liver events, hematologic events, drug interactions). Neurological events was the most frequent adverse reaction group; it appears that four patients had an interaction between omeprazole and their seizure medication and one patient was diagnosed with rolandic epilepsy.

7.0 DRUG INTERACTIONS

Omeprazole is metabolized by the cytochrome P-450 system. It is a substrate for isoenzymes 2C8, 2C18, and 2C19; an inhibitor of isoenzymes 2C8, 2C19, and 3A4; and an inducer for isoenzyme 1A2 (American College of Clinical Pharmacy [website=www.accp.com]). Therefore, omeprazole has the potential to interact

with other medications also affected by these systems. The labeling states that omeprazole can prolong elimination of diazepam, warfarin, and phenytoin and that clinical reports have been received regarding interactions with cyclosporine, disulfiram, and benzodiazepines.

The Adverse Event Reporting System (AERS) was searched as of March 31, 2000 using omeprazole as suspect and concomitant drug and *Drug interactions* as the MEDDRA PT term. The search produced a total of 209 reports. The individual cases were reviewed for those drugs that had five or more reports (i.e., digoxin, sertraline, divalproex sodium, conjugated estrogens, and fluconazole). Warfarin and cisapride had more than five reports, but they were excluded from this review because an interaction with warfarin is listed in the omeprazole labeling and cisapride has been withdrawn from the market.

A hands-on review of the reports for the drugs mentioned above found a signal of an interaction involving decreased effectiveness of conjugated estrogens (eight cases) when given concomitantly with omeprazole. There were eight cases of a return of menopausal symptoms (e.g., breast tenderness, hot flashes, breakthrough bleeding, uterine bleeding, and increased night sweats) when omeprazole and conjugated estrogens were given concomitantly. Eight reports, however, may not be enough to indicate a definite interaction. Additionally, a possible interaction involving decreased effectiveness of sertraline and divalproex sodium was noted when given concomitantly with omeprazole (three cases reported for each drug).

8.0 SERIOUS HEMATOLOGIC EVENTS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Marrow depression and hypoplastic anemias* and *agranulocytosis* as the MedDRA HLT and PT terms, respectively. The search produced 172 cases. These 172 cases were separated into domestic and foreign and checked for duplicates; only severe hematologic events (i.e., agranulocytosis, aplastic anemia, bone marrow suppression, pancytopenia, severe neutropenia [neutrophil count < 500]) were included for discussion. A total of 16 cases (5 domestic and 11 foreign) were excluded because they were nonserious hematologic events; the remaining 21 reports were duplicates. Thus, there were 47 domestic cases and 88 foreign cases available for review.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 47)

AGE (YEARS):	RANGE 17 to 85, MEAN 62 (n = 38)
SEX:	M (22), F (18), UK (7)
REPORTING YEAR:	1989 (1), 1990 (6), 1991 (4), 1992 (1), 1993 (8), 1994 (3), 1995 (2), 1996 (11), 1997 (2), 1998 (5), 1999 (3), UK (1)
REACTION ONSET (DAYS):	RANGE 4 to 1440, MEAN 142, MEDIAN 30 (n = 21)
DOSE PER DAY (MG):	20 MWF (1), 20 (28), 40 (4), 80 (1), 120 (1), UK (12)
DECHALLENGE POSITIVE:	17
RECHALLENGE POSITIVE:	1
OUTCOME*:	DIED(4), HOSP(25), LIFE-THREATENING(8), NONSERIOUS (4), OTHER (3), UK (9)
EVENT DESCRIPTION:	AGRANULOCYTOSIS (11), PANCYTOPENIA (24), APLASTIC ANEMIA (1), BONE MARROW SUPRESSION (6), MULTIPLE HEMATOLOGIC EVENTS (5)
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEMATOL. EVENTS†	27

* Some patients had multiple outcomes.

† Concomitant medications including allopurinol, amitryptyline, atenolol, captopril, carbamazepine, ceftazidine, cyclosporin, diclofenac, diltiazem, fluconazole, furosemide, isorsorbide, mesalamine, metoclopramide, metoprolol, metronidazole, nortriptyline, prochlorperazine, ranitidine, tobramycin, and vancomycin.

In addition to the Domestic cases that were individually reviewed, there were 88 foreign cases of serious hematologic events in AERS (agranulocytosis [37], pancytopenia [24], aplastic anemia [8], bone marrow supression [8], multiple hematologic events [11]).

Representative Case of Serious Hematologic Event

Case# 4735645 (direct report) \— 1990) A 69-year-old female developed pancytopenia and eventually died after taking 20 mg of omeprazole a day for 16 days to treat reflux esophagitis unresponsive to ranitidine. The patient had been admitted to the hospital for inflammatory bowel disease; her medical history included surgery for lower GI bleeding and adult respiratory distress syndrome. Her lab values after 14 days of omeprazole therapy were reported as follows: WBC 400; Hgb/Hct 10.1/30.1 mg%; and platelets 80,000/mm^3. She developed cellulitis with generalized septicemia and died of bacterial endocarditis 33 days after omeprazole was discontinued. Concomitant medications included corticosteroids, Flagyl, Pamelor, Rowasa, and TPN; she also received a blood transfusion. The reporter stated that her WBC did increase after omeprazole was discontinued.

8.1 Summary of Serious Hematologic Events

This section describes cases of serious hematologic events associated with the use of omeprazole. Pancytopenia (rare) and agranulocytosis (some fatal) are labeled events. Of the four domestic deaths, three patients were receiving medications known to cause hematologic events (one of those patients was taking an 80-mg dose of omeprazole per day) and the fourth patient had a history of bone marrow suppression while taking indomethacin. Overall, more than half (27 out of 47) of the patients were receiving medications know to cause hematologic events. Many reports described in this section lacked specific information (e.g., concomitant medications, lab values) making it difficult to determine causality or severity.

9.0 SERIOUS LIVER EVENTS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Hepatic disorders (exc neoplasms)* and *Liver transplant* as the MedDRA HLGT and PT terms, respectively. Domestic and foreign cases were searched separately. The search produced 208 domestic cases. These 208 cases were separated and checked for duplicates; only unduplicated cases with a serious outcome (i.e., death, life threatening, hospitalization, and disability) were included in this discussion (a total of 57 unduplicated domestic cases).

DEMOGRAPHIC DATA OF SERIOUS DOMESTIC CASES (n = 57)

AGE (YEARS):	RANGE 21 to 90, MEAN 59 (n = 45)
SEX:	M (23), F (28), UK (6)
REPORTING YEAR:	1989 (2), 1990 (10), 1991 (4), 1992 (9), 1993 (3), 1994 (6), 1995 (7), 1996 (5), 1997 (3), 1998 (6), 1999 (2)
REACTION ONSET (DAYS):	RANGE 1 to 730, MEAN 47, MEDIAN 15.5 (n = 36)
DOSE PER DAY (MG):	20 MG (35), 40 mg (5), 60 mg (1), 20-40 MG QOD (1), 20 INC. TO 40 MG (1), 20 mg QOD (1), UK (12)
DECHALLENGE POSITIVE:	25
RECHALLENGE POSITIVE:	1
OUTCOME:	DIED (8), LIFE-THREATENING (8), HOSP (40)*, DISABILITY (1)
EVENT DESCRIPTION:	HEPATITIS (14), HEPATIC FAILURE (16), JAUNDICE (14), MIXED EVENTS (HEPATOCELLULAR AND CHOLESTATIC) (13)
HISTORY OF ALCOHOL ABUSE	4
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEPATIC EVENTS†	24

* Two patients required liver transplants.

† Concomitant medications included acetaminophen, allopurinol, amitriptyline, ciprofloxacin, cisapride, clonidine, conjugated estrogen, Darvocet N, Diflucan, Dyazide, diltiazem, enalapril, famotidine, halogenated anesthesia, Hyzaar, Naprosyn, nifedipine, Noroxin, Pravachol, quinapril, ranitidine, steroids, thorazine, Vasotec, verapamil.

In addition to the domestic cases that were individually reviewed, there were 199 foreign cases. A hands-on review and a check for duplicates of the foreign cases was not performed; a report of MEDDRA SOC and PT terms was printed and reviewed. The following counts of serious events were noted: hepatic failure (25), hepatic necrosis (11), hepatitis (all types) (41), cholestatic jaundice (25), and jaundice (33).

Representative Case of Liver Failure

Case# 3387227 (Mfr# 199910200349) (IL, 1999) A 42-year-old female experienced acute liver failure requiring a liver transplant after taking 20 of omeprazole a day for approximately 3 months to treat GERD. The patient had had prior exposure to omeprazole (dose and duration unknown). She developed pruritus, anorexia, and jaundice with elevated SGOT (2165 Units/L), billirubin (10 mg/dL), and alkaline phosphatase (292 Units/L); an HIDA scan of the liver revealed poor uptake and a biopsy indicated massive hepatic necrosis with proliferation of cholangioles. There was no indication of autoimmune hepatitis; hepatitis A and B and herpes virus screens were negative. Her condition deteriorated; she developed Grade I-II hepatic encephalopathy and asterixis. The patient underwent a liver transplant and made an uneventful recovery. Her medical history included hypothyroidism; concomitant medication included Synthroid.

9.1 Summary of Serious Liver Events

This section describes cases of hepatic events possibly associated with the use of omeprazole. The hepatic events discussed in this section are labeled events. The categories in Event Description section above are mutually exclusive (e.g., a case of hepatitis leading to liver failure would be recorded as liver failure). Overall, these cases are more compelling (regarding severity and association with omeprazole) than the cases for other events described in this document. Of the eight deaths, five of the patients were receiving medications known to cause liver events and/or had underlying conditions (including alcohol abuse) that were more likely the cause of death. Two patients required a liver transplant; one case is described above and the other case did not provide much information, but the reporter did state that there was no cause for the patient's hepatitis other than omeprazole use. Four patients developed encephalopathy and four patients had hepatic necrosis. Overall, 24 patients (out of a total of 57 patients) were receiving medications also known to cause liver events; 4 patients had a history of alcohol abuse.

10.0 STEVENS-JOHNSON SYNDROME / TOXIC EPIDERMAL NECROLYSIS

Previously, HFD-180 received a Monitored Adverse Reaction Report concerning severe skin reactions associated with omeprazole dated October 19, 1992, which presented two cases of Stevens-Johnson Syndrome (SJS) and three cases of toxic epidermal necrolysis (TEN) (Attachment B). This section updates that previous information.

AERS was searched for reports of SJS or TEN (MedDRA preferred terms [PT] STEVENS JOHNSON SYNDROME and EPIDERMAL NECROLYSIS) involving omeprazole that were received by the FDA from October 1, 1992 up through and including March 31, 2000. A total of 84 reports were retrieved, which represented 49 unduplicated cases. Forty-two of these cases were from foreign sources, primarily Germany (25), which is performing an extensive epidemiological study regarding severe skin reactions and maintains a registry of patients.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 7)

AGE (YEARS) (n = 6):	Range—47 to 72 years; Median—53 years; Mean—55.7 SEX (n = 6): Female—2; Male—4
EVENT DATE:	1993, 1995, 1996—1 each; 1997—2; 1998—1; Unknown—1
REACTION ONSET (DAYS) (n=4):	Range—1.5 to 120 (approx.) days; Median—23.5 days; Mean—42.1 days (approx.)
DOSE PER DAY (n = 6):	20 mg—5; 40 mg—1
DECHALLANGE:	Positive—5; Negative—1; Unknown—1
OUTCOME:	Hospitalized—2; Non-serious—4; Unknown—1
REACTION (n = 6):	SJS—4; TEN—1; SJS/TEN—1

Two of the cases had very minimal information; one noting that the patient was admitted to the hospital with "Stevens-Johnson like syndrome," and the other, from a physician reporter, stating the patient came to his office saying "a combination of Prilosec and Dilantin caused Steven-Johnson syndrome." One case had a negative dechallenge in that the patient's rash continued to wax and wane for several weeks following discontinuation of the drug. Also in this case, a confirmed diagnosis was never made; the patient claimed he possibly had a mild case of TEN. There was a well-documented case of TEN, but it's possible that ranitidine, which lists erythema multiforme in its labeling, may have contributed to the reaction. In that case, the patient originally developed a rash while on omeprazole, which was then discontinued and replaced with ranitidine. The rash initially improved, but then progressed after about three weeks of ranitidine therapy, eventually developing into TEN.

Representative case of Stevens Johnson Syndrome

Case# 3300119 (Mfr.# 19980900019) A 47-year-old female with reflux esophagitis, esophageal stricture and hiatal hernia was placed on omeprazole 20 mg twice a day on [redacted] for the treatment of gastroesophageal reflux disease. Concomitant therapy included loratidine and levothyroxine. Five days later, the patient experienced pruritis, which was worse on the hands. Four days after that, the rash had worsened and the patient discontinued omeprazole. Two days later, her physician noted that there were multiple wheel-like bulls-eye lesions on the posterior and anterior aspect of the trunk. There was involvement, to a lesser extent, on the patient's extremities. Additionally, there were several superficially ulcerated areas on her tongue. There was some ecchymotic involvement on the soft palate and some erythematous areas on the posterior pharynx. The patient was diagnosed with probable Stevens-Johnson syndrome. The patient was treated with hydroxyzine, prednisone, and triazolam. Ranitidine was also started for the treatment of reflux. The patient had improved five days after beginning treatment. The rash changed from primarily papular and vesicular to macular, especially on her back and chest, and these areas had begun to scale. There was no further involvement of the oral mucosa and her lips were less swollen.

10.1 Summary of SJS and TEN Cases

One or two domestic cases per year have been reported since the previous document was issued. Of the seven updated domestic cases, three could be considered compelling for an association between the events and omeprazole. None of these cases were fatal. Additionally, there does not appear to be an increase in the reporting of this event since the last consult. The current labeling includes TEN and SJS, noting that some reactions have been severe and fatal.

11.0 VENTRICULAR ARRHYTHMIAS

AERS was searched for reports of ventricular arrhythmias associated with the use of omeprazole that were received by the FDA up through and including March 31, 2000 using the OPDRA Reaction Group VENT ARRHYTHMIAS. This grouping includes the terms VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST (HLGT), ELECTROCARDIOGRAM QT PROLONGED (PT), ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED (PT), and ELECTROCARDIOGRAM QRS COMPLEX PROLONGED (PT). A total of 92 reports were retrieved, which represented 76 unduplicated cases. From these 76 cases, 1 was excluded because it involved a report of a medication error in which the patient received Prozac instead of Prilosec. An additional 16 cases were excluded after reviewing them as the association with omeprazole was poor (negative dechallenge, poor temporal relationship, other causes). Three cases, all of them deaths, were not included in the demographics as ventricular arrhythmias per se were not documented, although the deaths were stated as due to cardiac arrest or possible cardiac arrest. Two of those cases involved the use of cisapride and the other one involved the use of amitriptyline, which are all metabolized through the cytochrome P450 system. There were 32 foreign cases in the AERS database. The remaining 24 domestic cases are summarized below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 24)

AGE (n = 18):	Range—7 to 71 years; Median—49.5 years; Mean—48.1 years
SEX (n = 20):	Female—11; Male—9
EVENT DATE:	1990, 92, 93, 94, 95—1 each; 1996—4; 1997—4; 1998—4; 1999—1; Unknown—6
REACTION ONSET (n=9):	Range- 1-60 days; Median-9; Mean 19
DOSE PER DAY (n = 15):	20 mg—12; 40 mg—2; 60mg—1
DECHALLANGE:	Positive—7; Unknown—17
OUTCOME:	Death—5; Hospitalized (or prolonged)—8; Non-serious—7; Unknown—4
REACTION:	Prolonged QT interval—8 PVCs—5 Torsade de pointes—4 Ventricular tachycardia—4 Ventricular fibrillation—4 Palpitations—3 Paroxysmal atrial tachycardia—1 Ventricular bigeminy—1

he reaction total is greater than 24 as some cases listed more than one event.

Regarding onset of event, five of the nine cases involved a potential drug interaction; onset was calculated in relationship to omeprazole initiation. In one of the cases, the patient had been on the drug for 13 months, but experienced the event 4 days after the dose was increased from 20 mg once to 20 mg twice daily. At the same time, the cisapride dose was increased from 30 mg to 40 mg daily (in this case onset was counted as 4 days). In another case, the patient had been taking the drug for 49 days when symptoms appeared (palpitations/syncope); at day 62 of therapy an ECG showed PVCs (in this case onset was counted as 49 days).

Eleven of the 24 cases were potentially due to a drug interaction. Cisapride was involved in six of these cases. Of the four torsade de pointes cases, three included the concomitant use of cisapride. Other potential drug interactions included amiodarone, terfenadine, nelfinavir, clarithromycin, and nicardipine.

Representative Case: Prolongation of QT interval

Case# 3152050 USA
A 55-year-old male with a history of a kidney transplant and CAD, was admitted to the hospital on —— already on cisapride 10 mg four times a day for chest pain. On — the patient was started on omeprazole 20 mg once a day for symptoms of GERD. Baseline ECG on — showed a QT interval of 400 msec. After receiving three doses of omeprazole the QT interval on — was 500 msec. Omeprazole was stopped and replaced with famotidine. On — the QT interval was back to baseline at 380 msec.

11.1 Summary of Ventricular Arrhythmia Cases

Of the 16 cases involving a serious arrhythmia (increased QT interval, torsade de pointes, ventricular fibrillation, ventricular tachycardia), 11 were potentially due to a drug interaction, principally with cisapride (6). Of the 13 cases in which there was no interacting drug mentioned, 8 were non-serious arrhythmias including PVCs, palpitations, ventricular bigeminy, and paroxysmal atrial tachycardia. It appears omeprazole has the potential for causing certain arrhythmias (tachycardia, bradycardia, and palpitation are listed in the product labeling). The risk for serious arrhythmias may be increased when used with interacting drugs that are known to produce such arrhythmias (e.g., cisapride). However, the data from AERS is not supportive of a clear relationship of omeprazole independently to cause such serious ventricular arrhythmias, and cisapride is no longer available on the general market.

12.0 PANCREATITIS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Pancreatitis* and *Digestive enzymes* as the MedDRA HLT terms. The search produced 126 cases. These 126 cases were separated into domestic and foreign and checked for duplicates. A total of 3 cases were excluded because they were miscoded and 34 reports were duplicates. Thus, there were 62 unduplicated domestic cases and 27 unduplicated foreign cases for review.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 62)

AGE (YEARS):	RANGE 3 TO 85, MEAN 52 (n = 46)
SEX:	M (29), F (26), UK (7)
REPORTING YEAR:	1989 (1), 1991 (5), 1992 (2), 1994 (1), 1995 (6), 1996 (11), 1997 (15), 1998 (14), 1999 (3), 2000 (1), UK (3)
REACTION ONSET (DAYS):	RANGE 2 TO 540, MEAN 131, MEDIAN 51
DOSE PER DAY (MG):	10 (1), 20 (47), 40 (1), 60 (1), 20 QOD (1), UK (11)
DECHALLENGE POSITIVE:	24
RECHALLENGE POSITIVE:	2
OUTCOME*:	DIED (2), HOSP (41), NONSERIOUS (12), LIFE-THREATENING (3), RECOVERED (1), UK (5)
EVENT DESCRIPTION:	PANREATITIS (58), ELEVATED AMYLASE AND/OR LIPASE (4)†
PTS WITH HISTORY OF ALCOHOL ABUSE	3
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE PANCREATIC EVENTS‡	13

* Several patients had multiple outcomes.
† Two of these patients had clinical symptoms of pancreatitis as well as elevated amylase and/or lipase, but reporter did not specify that the patient had pancreatitis.
‡ Concomitant medications including furosemide, lisinopril, prednisone, divalprox, estrogens, Prozac, Voltaren XR, Zestril, valproic acid, and Procardia.

In addition to the Domestic cases that were individually reviewed, there were 27 foreign cases of pancreatitis in AERS; 7 of those cases resulted in death from other causes. (Note that four patients were receiving IV omeprazole.)

Representative Case of Pancreatitis

Case# 4733766 (Mfr# [redacted] 1990) A male (age unknown) developed an ileus one week after taking an unknown dose of omeprazole to treat duodenal ulcer; he subsequently developed pancreatitis, underwent surgery, and eventually died. His medical history included thrombocytopenia; concomitant medications included Augmentin, Lasix, and unspecified steroids.

12.1 Summary of Pancreatitis Cases

This section describes 62 cases of pancreatitis possibly associated with the use of omeprazole. Pancreatitis (some fatal) is a labeled event. Two domestic deaths were reported; one case is described above and the other case provided even less information. Eight patients were reported to have acute pancreatitis (including one of the patients that died) and one patient was reported to have hemorrhagic pancreatitis. Of these nine cases, three patients were receiving concomitant medications known to cause pancreatitis, two patients had a history of pancreatic problems, one patient had a history of alcohol abuse, and one patient's pancreatitis was attributed (by the physician) to gallstones. Overall, 13 of the 62 patients were receiving medications known to cause pancreatitis, 3 patients had a history of alcohol abuse, and 4 patients had a history of pancreatic problems. Many reports described in this section lacked relevant information (e.g., concomitant medications, lab values) making it difficult to assess causality or severity.

13.0 OPHTHALMOLOGIC EVENTS

This section also responds to a consult dated February 17, 2000 from HFD-180 for a search of the AERS database for cases of visual disturbances associated with the use of omeprazole. The purpose of that request was to provide documentation for the addition of "blurred vision" and "eye irritation" to the Adverse Reactions section of the omeprazole labeling, as requested by the manufacturer.

Note that three previous consults have been completed at HFD-180's request regarding this issue (see Attachments C, D, and E). The case inclusion date for the most recent consult (Attachment E) was April 28, 1998. The reader is encouraged to review these previous documents.

To update the previous consults, AERS was searched using omeprazole as suspect drug and *Eye Disorders* as the MedDRA System Organ Class (SOC) term. This search produced a total of 351 reports. A listing of the eye events with 10 or more cases is presented below (some of these numbers may represent duplicate reporting). In order to evaluate the most severe outcome of an ophthalmic event, a second search using omeprazole as suspect drug and *Blindness HLT* as the MedDRA High Level Term (HLT) was performed from the time of marketing to March 31, 2000. This search produced a total of 31 reports. There were 11 domestic blindness cases; a hands-on review of these was conducted.

SOC EYE DISORDERS: EVENTS WITH 10 OR MORE CASES (U.S. PLUS FOREIGN)

Vision abnormal NEC	63
Vision blurred	40
Dry eye NEC	28
Eye disorder NOS	20
Visual distrubance	20
Visual acuity reduced	17
Eye pain	15
Diplopia	15
Papilledema	14
Optic atrophy	13

DEMOGRAPHIC DATA FOR U.S. BLINDNESS CASES (n = 11)

AGE (YEARS):	66 MEAN (RANGE 39 to 81)
SEX:	M (2), F (9)
YEAR OF EVENT:	1989 (1), 1993 (1), 1994 (2), 1997 (5), 1998 (2)
REACTION ONSET:	1 DOSE (2), 2 DAYS (1), 8 DAYS (1), 38 DAYS (1), >1.5 YEARS (3), UK (3)
ORAL DOSE PER DAY:	20 MG (7), 20-40MG (1), 40MG (1), UK (2)
DECHALLENGE:	POSITIVE (1), NEGATIVE (1)
RECHALLENGE:	POSITIVE (1)

~~SERIOUS OUTCOME RELATED TO OPHTHAL. EVENT: HOSPITALIZED (2), DISABLED (4)~~

The following three blindness cases are domestic cases received since the last consult of April 23, 1998

Case# 3300292 (Mfr# 19980600094) (U.S. [consumer], 1998) A 61-year-old female was driving and became unable to see out of her left eye after taking omeprazole 20 mg for one day to treat "reflux." She also experienced dizziness. Her blindness abated (timeframe unknown); she continued omeprazole therapy. Her concomitant medications and medical conditions were not reported.

Case# 3130343 (Mfr# 19980500646) (NY, 1997) A 68-year-old female experienced temporary loss of vision lasting for several minutes after taking one dose of omeprazole 20 mg to treat GERD and *Helicobacter pylori*. Omeprazole was discontinued and the event abated. Concomitant medications included Lasix, Zestril, Coumadin, and Lanoxin; she also received Biaxin and Tritec, but temporal relationship to omeprazole therapy was not specified. Her medical history included chronic atrial fibrillation, hypertension, other disorders of the esophagus, and allergy to Naprosyn (caused rash).

Case# 3295045 (Mfr# 19980300172) (WV, reported 1998) An 81-year-old female developed blindness after taking omeprazole 20 mg every 2 to 3 days for "several years" to treat GERD. The event abated after omeprazole was discontinued. Her medical history included macular degeneration; muscle spasm reaction to cimetidine; visual difficulties from lansoprazole, cisapride, and famotidine; and allergies to sulfa, penicillin, neosporin, and novacaine. Concomitant medications included Prevacid, Propulsid, and Pepcid.

13.1 Summary of Ophthalmologic Events

This information updates three previous consults regarding omeprazole and ophthalmic events. OPDRA was asked specifically about AERS cases of blurred vision and eye irritation, as these relate to a manufacturer's request for labeling change. In addition, we looked at cases of blindness received through AERS since the time of marketing. From the recent printout of all visual disturbances associated with omeprazole use, there are a total of 40 reports of *Vision blurred*. There are a total of 5 reports of *Eye irritation NOS* in AERS. Note that eye irritation also could include other PT terms such as *Eye Pain* (15 cases), *Eye inflammation* (1 case), *Dry eye NEC* (28 cases), *Conjunctivitis NEC* (18 cases), as well as other terms. It appears that we continue to receive AERS reports of blurred vision, eye irritation and other ophthalmologic events associated with the use of omeprazole. However, it is difficult to establish a clear relationship between omeprazole use and these events, particularly because of the extensive use of omeprazole in the U.S. as well as the prevalence of general vision disorders.

It would appear reasonable to allow the sponsor to include blurred vision and eye irritation in the omeprazole labeling, although the relationship appears inconclusive. A general term, such as "visual distrubance" or "abnormal vision" might also be considered to reflect the reporting of such cases (Vision abnormal NEC: 63 cases, Visual distrubance: 20 cases, Visual acuity reduced: 17 cases). Although blindness cases have been

reported, analysis of these do not support a relationship to omeprazole; no labeling recommendation regarding blindness can be made at this time.

14.0 HEARING DISORDERS

AERS was searched for reports of hearing disorders associated with the use of omeprazole that were received by the FDA up through and including March 31, 2000. Terms used for the search were HEARING DISORDERS (HLGT), INNER EAR & VIIIth CRANIAL NERVE DISORDERS (HLGT), and MISCELLANEOUS EAR DISORDERS (HLGT). A total of 167 reports were retrieved, which represented 158 unduplicated cases. Twenty-six cases were excluded after reviewing them as the association with omeprazole was poor (poor temporal relationship, other causes [e.g., salicylate intoxication, acoustic neuroma, earwax]). There were 22 foreign cases in the AERS database. The remaining 110 domestic cases are summarized below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 110)

AGE (n = 83):	Range—6 to 89 years; Median—54 years; Mean—54.6 years
SEX (n = 100):	Female—64; Male—36
EVENT DATE (n = 76):	1989—2 1995—9 1990—5 1996—9 1991—4 1997—15 1992—1 1998—17 1993—10 1999—2 1994—2
REACTION ONSET (n = 57):	Range—1 day to approx. 3.5 years; Median—approx. 6 days; Mean—approx. 100.6 days
DOSE PER DAY (n = 70):	5 mg—1; 20 mg—54; 40 mg—15
DECHALLANGE/RECHALLENGE:	Dechallenge positive—49 Dechallenge negative—16 Rechallenge positive—6 Rechallenge negative—1
OUTCOME:	Non-serious—100; Disability—5; Hospitalized—1; Unknown—4
REACTION:	Tinnitus—68 Vertigo—21 Hearing loss—17 Dizziness—14 Ear pain—10 "Ototoxicity" (undefined)—2

The reaction total is greater than 110 as some cases listed more than one event.

A review of the cases of ***hearing loss*** (n = 17) showed the following demographics:

AGE (n = 15):	Range—6 to 74 years; Median—49 years; Mean—47.3 years
SEX (n = 17):	Female—8; Male—9
REACTION ONSET (n = 11):	Range—1 day to approx. 6.5 months; Median—approx. 5 days; Mean—approx. 25.4 days
DOSE PER DAY (n = 10):	5 mg—1; 20 mg—7; 40 mg—2
DECHALLENGE:	Dechallenge positive—11 Dechallenge negative—3
OUTCOME (n = 15):	Non-serious—11; Disability—3; Required intervention (Rx)—1

Representative Case of Hearing Loss

Case# 5499583; Mfr.# 19950900131 (USA, 1995) A 42-year-old male physician with no known allergies was placed on omeprazole 20 mg daily for the treatment of GERD on ——— There were no concomitant medications reported. On ——— the patient experienced decreased auditory acuity. Audiometric exam revealed a unilateral sensory deficit, and an MRI was negative. Omeprazole was discontinued on ——— and since that time his hearing has improved slightly.

There did not appear to be an appreciable difference in the characteristics of the patients who developed HL compared to the group as a whole, although they tended to be younger in age. The majority of HL cases (65%) exhibited a positive dechallenge with the patient either returning to baseline or showing an improvement in symptoms.

An attempt was made to determine from all cases with a negative dechallenge (n = 16), which might indicate a permanent hearing disorder, if they could be associated with a longer duration of therapy. In those negative dechallenge cases in which a reaction onset could be determined (n = 7), the median time to onset was 72 days with a mean of 108.4 days, which could imply that a longer duration of therapy may lead to permanent damage, although additional follow-up in those patients might prove otherwise. On the other hand, in the four patients who had a reaction after years of therapy (two cases of tinnitus, one case each of vertigo and ear pain), three had a positive dechallenge (unknown for one case of tinnitus). In the three patients with HL who had a negative dechallenge, there was not enough information to make a determination regarding length of therapy and permanent HL. Two of these patients were considered to have a permanent disability, which occurred after approximately six weeks and six and a half months of therapy, respectively. The third patient's condition was described as persisting 10 days following discontinuation of omeprazole, which he had taken for approximately 9 days. In those HL patients with a positive dechallenge, reaction onset ranged from one to seven days following initiation of therapy. Therefore, in cases of hearing loss, it might appear that a longer duration of therapy may lead to permanent damage, but this is a tenuous assumption based on only two cases.

14.1 Summary of Hearing Disorder Events

Regarding the 110 domestic cases, the vast majority (91%) had a non-serious outcome and in 45% of the cases there was documentation of improvement in the hearing disorder after omeprazole was discontinued (positive dechallenge). Tinnitus and vertigo represented the most frequently submitted reports and both are listed in the product labeling along with dizziness. Hearing loss (HL) and ear pain are not specifically listed in the product labeling and accounted for 17 and 10 reports, respectively. The 17 hearing loss cases were mainly reversible; there was not a strong signal for hearing loss association with omeprazole. Further, an attempt was made to relate duration of omeprazole use to nonreversible hearing disorders by reviewing 17 cases with negative dechallenge. Although a trend was seen with the nonserious cases, only two hearing loss cases seemed to bear this relationship.

15.0 CANCER

A July 30, 1999 memorandum summarized a review of the medical literature and worldwide post-marketing reports for tumors associated with proton pump inhibitors including omeprazole. The medical literature review included a discussion of toxicological studies in rats, mice and dogs that showed generalized hyperplasia of the gastric mucosa. No human studies were identified in the search that proved carcinogenesis. This document also described 362 AERS reports of neoplasms, benign and malignant as of 7/13/99[1]. Among

[1] Correction of previous document information: total number of AERS reports for omeprazole as of 7/13/99 was approximately 8400; number of U.S. cases of neoplasms (all types) was approximately 180. These numbers may include duplicate reporting.

these domestic and foreign cases, age and gender information was available in 276; 45% were female and 39% were considered elderly. The 85 case report forms of domestic and foreign GI neoplasms were retrieved and 54 unduplicated U.S. cases were analyzed; neoplasms reported included gastric polyps (19), gastric cancer (14) and gastric carcinoids (9). This document is included as Attachment F.

15.1 CANCER REPORTS IN AERS

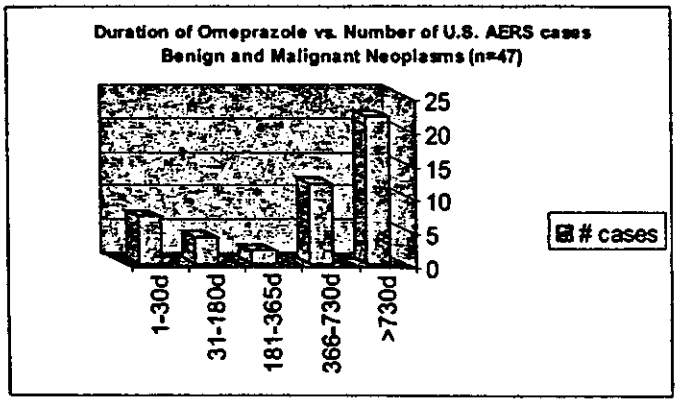
Two updated AERS searches (data as of 3/31/2000) were performed relating to cases of cancer. The first search included the SOC Neoplasms benign and malignant (including cysts and polyps). This broad search revealed a total of 456 cases. Two hundred fifteen (215) were domestic, 236 were foreign and in 77 reporter country was unknown. Neoplasm events of any nature among the 456 cases which had counts of 5 or more are presented below (some may be duplicates):

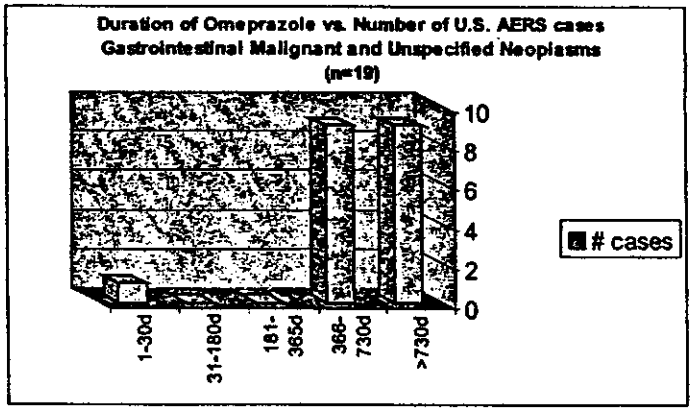
Neoplasm NOS	54
Gastrointestinal tract cancer NOS	40
Carcinoma NOS	20
Gastric polyps	16
Gastrointestinal neoplasm NOS	12
Carcinoid tumor of the stomach	10
Lymphoma NOS	8
Carcinoid tumor NOS	6
Cyst NOS	5

The second search utilized the HLGT Gastrointestinal neoplasms malignant and unspecified, which revealed 171 cases, 78 of which were from the U.S. (domestic). The domestic cases of all cancers and gastrointestinal cancers were further analyzed to relate duration of use to numbers of reported cases of cancer. Duration was a computer-based calculation, which used the following algorithm:

Number of days duration = Start Date of omeprazole to End Date of omeprazole (if no End Date was present, Event Start Date was utilized).

Since this calculation depended on the specific data fields being populated in the reports, this did not result in a large data set. Of the 215 total domestic cases, 47 had sufficient data; of the 78 total GI cases, only 19 had sufficient data to perform the duration calculation. The results are presented graphically below. There is a general trend for larger numbers of reports with a longer duration of use, however, conclusions would be difficult to draw as this data is derived from small numbers from a spontaneous reporting system, which is subject to various reporting biases.





15.2 CANCER DATA IN THE LITERATURE

An updated review of the literature was obtained June 2000 to look for case reports of cancer or incidence studies of Omeprazole-related cancer. The following databases were searched: MEDLINE, Embase, Derwent Drug File, IPA, Biosis, Life Sciences, and CANCERLIT. A few possible cases of omeprazole-related cancers were identified in the literature review. A 31-year-old man who had received four courses of antiulcer drugs (famotidine, omeprazole, and lansoprazole) over 38 months developed an argyrophil-positive carcinoid tumor (1). Three patients with severe exudative distal esophagitis were diagnosed with invasive adenocarcinoma within one year of continuous omeprazole treatment (2).

A recent comprehensive review article by Laine et al summarizing animal studies and short- and long-term human studies asserts that omeprazole rarely produces adverse events (3). Since most cancers generally have long latency periods, with gastric cancer reported to have a latency period greater than 15 years (4), a special search for long-term studies was completed to look for cancer incidence. Five long-term (> 12 months of treatment) studies of omeprazole were reviewed (Table 1) (5-9). These studies were conducted outside the United States and may have overlapping patient populations (the methods sections provide limited patient population descriptions). Most of the investigators of these studies also received funding from the sponsor. The longest period of treatment for any study group was 11 years - short of the time needed to study omeprazole-related cancers. No histologically proven gastric cancer cases were reported in any of these

studies. Two possible cases of cancers were reported by Lloyd-Davies et al - one patient diagnosed with primary pancreatic and duodenal tumor after an undefined period of drug exposure and another patient diagnosed with lymph node metastasis without an identified primary tumor and an undefined drug exposure (8). Klinkenberg-Knol et al reported a case of Barrett's carcinoma diagnosed in a 75-year-old man who had a Barrett's ulcer at study entry (9). Six other carcinomas, none of them gastric, were reported in this same study(9).

The long-term studies of omeprazole-related cancer that have been published are limited by three important factors – study size, exposure time, and duration of follow-up. A study of omeprazole-related cancer requires a large number of patients and an extended period of follow-up since gastric cancer is not common, only 22,000 cases of gastric cancer occur in the United States each year (10), and has a long latency period. The studies reviewed have limited number of patients exposed for short time periods and limited follow-ups. The study of omeprazole-related cancer requires extended cohort or nested case control designs that include adjustments for potential confounders, such as underlying disease and smoking. None of the studies in the literature meet this criteria.

Table 1. Summary of Long-term Studies of Omeprazole Cancer Outcomes

Study	No. of Patients	Patient Population	Range of Treatment (No. Range)	Dose	No. of Cancer Cases
Lloyd-Davies KA et al 1988*	80	Zollinger-Ellison	< 1 month – 4 yrs; mean 19 months	260 - 360 mg (median 60 – 70 mg)	1 - Pancreatic and duodenal carcinoma 1 – lymph node metastasis
Joelson S et al 1992*	859	Poorly responsive peptic ulcer or oesphagitis	Up to 6 years	NL	0
Solcia E et al 1992*	448	Peptic ulcer, anastomotic ulcer, or reflux oesophagitis	Up to 4 years	20 - 40 mg	0
Lamberts R et al 1993	74	Chronic esophageal, gastric, or duodenal ulcerations resistant to other treatment	6 months – 7 yrs; median 48 months	40 - 60 mg	0
Klinkenberg -Knol EC et al 2000*	230	Persistent reflux esophagitis	Up to 11 years; mean 6.5 years	10 – 120 mg	1 - Barrett's ca and 6 - non-gastric carcinomas

* Astra Hässle AB either listed as an author or source of funding for the study

16.0 DELAYS IN DIAGNOSIS

Concerns about possible delays in diagnosis exist because the symptoms of gastric cancer can be similar to those of peptic ulcer and thus attempts at medical treatment may be initiated without diagnostic work-ups (11, 12). Diagnostic delays related to cimetidine have been reported in the literature in the past and can be instructive when considering diagnostic delays related to omeprazole. Stoddard et al reviewed the cases of adenocarcinoma of the stomach diagnosed in their unit from August 1979 to May 1980. Investigators identified 12 of 29 patients with delays between 2 and 12 months; 8 of the 12 patients had been treated with cimetidine and antacids for up to 12 months before surgical referral (13). Another group of investigators from the United Kingdom searched the Cambridge Cancer Registration Bureau to identify patients with gastric carcinoma presenting to their hospital between 1978 and 1980 (12). Medical records were reviewed and general practitioners interviewed patients (if necessary) to obtain information about the 100 cases identified. Sixteen patients received cimetidine before diagnosis (duration of therapy varied from 1 to 13 months). Five of the 16 received cimetidine without an upper gastrointestinal barium study or endoscopy.

Mikulin et al more recently interviewed all patients identified with gastric cancer in Nottingham from October 1981 and September 1982 (14). Eighty-three patients (mean age 71 years) were asked about their symptoms and management histories. Fifty-three (64%) of the patients received medication prior to diagnosis, 24 of whom had no investigation prior to drug therapy, 17 of whom received cimetidine. There was no difference in the median days of delay to treatment among those receiving cimetidine (6 weeks) and those receiving antacids (5 weeks).

Of special concern related to drugs used to treat dyspepsia are the case reports of patients who show improvement with drug treatment, delay further diagnostic work-up, and later are identified as patients with gastric cancer. Mikulin et al describes 3 patients who had benign gastric ulcers diagnosed, were treated with cimetidine, and showed improvement of their symptoms (14). All three patients relapsed and were found to have gastric cancer. Wayman et al reports a case series of 7 patients who participated in a special endoscopy protocol (15). Patients in this study had an initial endoscopy, were then started on proton pump inhibitors, and underwent a second endoscopy to ensure resolution of any biopsied ulcer. The 7 patients were found to have ulcerating early gastric cancer when the second endoscopy was performed, but only after inadvertently receiving a short course of a proton pump inhibitor that produced an asymptomatic state. Given the resulting asymptomatic state these patients might have experienced further diagnostic delays if they had not been participated in this study, but instead just initiated medical therapy.

All these papers were conducted by English authors and may not be generalizable to the United States where medical manangement may differ. These papers emphasize, though, that even medical experts have delayed the diagnosis or mis-diagnosed gastric cancer and used a variety of drugs in lieu of or despite a diagnostic work-up. At least one study suggests that the delays in diagnosis were not different for over the counter treatments (antacids) versus prescription treatments (cimetidine) (14). Future studies of delays in diagnosis related to over the counter omeprazole should be done and could use similar methods to these referenced studies.

18.0 DISCUSSION/CONCLUSION

This consult was prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review selected adverse events for omeprazole as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole up to March 31, 2000; 10,005 reports were identified in the database. Both domestic and foreign experience is addressed in this document, however, the focus is on the domestic experience. The following issues have been reviewed in this consult: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For many of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole; many patients had underlying conditions or were taking concomitant medications which could have contributed to the events. Summary of these issues appears at the end of each section. The most compelling issue reviewed was serious liver events, which were temporally related to omeprazole use and included serious outcomes such as liver transplants, deaths, and encephalopathy. Serious liver events are included in the current labeling for omeprazole. The pediatric cases reviewed tended to mirror events seen in adults; these typically were not healthy children prior to omeprazole use.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that there was a trend for larger numbers of reports with a longer duration of omeprazole use, however, conclusions cannot be made because the data was derived from small numbers of spontaneous reports in the system. A review of the studies and case reports in the literature for omeprazole-related cancer revealed that the studies had limited numbers of patients exposed for short time periods with limited follow-ups. A review of the literature for delays in GI cancer diagnosis due to patient self-medication revealed that both prescription and OTC use of antacid drugs may delay diagnosis; additional studies are needed. Data regarding congenital anomalies will be addressed in a separate document.

Given the number of years that omeprazole has been on the market (11 years) and its extensive use (——— prescriptions), AERS report data suggest that the frequency of serious adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, underreporting must be considered.

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APPEARS
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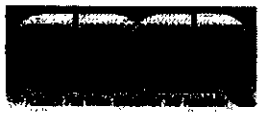


OTC MEDICAL OFFICER'S REVIEW

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

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

Table of Contents:

Executive Summary:

I. Recommendations

Recommendation on Approvability

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

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

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

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

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

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

B. Efficacy

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

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

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

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

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

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

C. Safety

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

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

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

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

D. Dosing

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

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

E. Special Populations

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

Clinical Review:

I. Introduction and Background

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

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

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

- The efficacy, appropriate dose and duration of therapy, and use of Prilosec1 in the OTC setting were not adequately established. The ability of the consumer to appropriately self-select and to use Prilosec1 safely and effectively in the OTC setting had not been demonstrated.
- The data had not adequately demonstrated the ability of consumers to comprehend the risks associated with specific drug interactions, nor the ability of consumers to avoid concomitant use of specific interacting drugs without the intervention of a physician.
- The sponsor did not provide adequate safety information to support OTC omeprazole use in individuals under the age of 18 years, or the risks to the fetus of potential Prilosec1 use in the OTC setting by women who are pregnant or of childbearing potential.

- The sponsor also was requested to establish that consumers would not use Prilosec1 for extended periods of time without contacting a health care provider.

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

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

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

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

Adults 18 years of age and older:

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

There are two classes of drugs available OTC for heartburn relief: antacids and histamine-2 receptor antagonists (H_2RA, acid reducers). They are indicated for relief of heartburn symptoms. In addition, H_2RAs are approved for prevention of heartburn symptoms induced by meal. The list of currently available OTC drug products for the treatment and prevention of heartburn symptoms is presented in Table 2 below.

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

Proprietary (pharmacological) Name	NDA/ANDA Number*	Pharmacological Category
Zantac 75 (ranitidine HCl)	20-520	H_2RA
Tagamet HB (cimetidine)	20-951	H_2RA
Pepsid AC (famotidine)	20-325	H_2RA
Axid AR (nizatidine)	20-555	H_2RA
Pepsid Complete (calcium carbonate, famotidine, magnesium hydroxide)	20-958	Combination Product
Gaviscon (aluminum hydroxide, magnesium trisilate)	18-685	Antacid Combination
Various trade names (Calcium carbonate; Aluminum hydroxide; Magnesium salts; Sodium bicarbonate, in combination or as single ingredients)	Final Monograph for Antacid Products for OTC Human Use	Antacids

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

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

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

III. Human Pharmacokinetics and Pharmacodynamics

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

IV. Description of Clinical Data and Sources

In support of this application, the sponsor has submitted the following information:
1. Results of the Actual Use Trial (#007),
2. Results of three Label Comprehension studies (#02255, #12179, #17859),
3. Proposed OTC labeling for 20 mg omeprazole magnesium tablet, and
4. Safety update.

V. Clinical Review Methods

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

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

VI. Integrated Review of Efficacy

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

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

Study Objective

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

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

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

Study Design

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

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

Visit 1

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

All consumers presenting to the shopping centers were assigned an identification number and were asked:
"We are conducting a research study to determine consumer's reactions to a proposed new over-the-counter heartburn medication. Do you get heartburn?"

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

When they had finished examining the package, subjects were then asked:
"Do you think Prilosec1 is a medication you could use for your heartburn?"

After the self-selection decision had been made, study personnel captured each consumer's decision (yes, no) and reasons word-for-word (verbatim). Subjects who self-selected that the study medication was one they could use for their heartburn were then asked:
"You indicated that Prilosec1 is a medication you could use for your heartburn. We are looking for people to participate in a research study to learn how people use this new heartburn medication. To be in the study you must:
1) buy the study medication today which sells for $12.00 for 14 tablets,
2) write down in a diary each time you take the medication,
3) when finished, mail the dairy back to us in a postage-paid envelope, and
4) return for an end-of-study visit.
You will be given $100 for completing the study in addition to the $20 for today's interview.
Would you like to participate in this study?"

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

Subject enrollment ceased when approximately 850 subjects had purchased study medication. Pricing was representative of proposed market prices ($12.00 for a 14-count carton). Study medication was supplied as a carton of pink/rust tablets packaged in blister cards, each carton containing 14 tablets. The carton simulated the proposed OTC market-ready packages of Prilosec1 and contained proposed OTC use directions on the back carton panel as well as the package insert. The retail display of Prilosec1 also contained both educational materials specific to Prilosec1 and heartburn. These materials

were available for the subjects to pick up if they chose, but were not distributed by the study staff.

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

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

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

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

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

The informed consent form was given after the self-selection decision has been made. The consent form has been reviewed and was found to be acceptable. The fact that subjects were aware that they would be paid prior to their enrollment may have influenced their responses to the subsequent questionnaires.

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

Purchase Criteria

To be allowed to purchase study medication, subjects must:

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

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

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

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

Comments:

Inclusion and exclusion criteria were minimized and were applied after the self-selection was made. It is reasonable to exclude from the study, subjects who are at risk, after the self-selection was determined. Those who were excluded by the investigator because of their risk should have been counted as a self-selection failures.

Table 3 lists the schedule of events of the study.

Table 3. Study-Specific Procedures Performed at Each Visit

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

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

Eligible subjects were given the opportunity to purchase additional cartons of the study medication (limit 4 cartons). Subjects were not told of the 4-carton limit until such time that they requested to purchase more than 4 cartons (56 tablets). Should subjects wish to

purchase additional study medication after the first visit, they may have done so during retail hours at the same location, and were asked about contact with medical personnel at the time of repurchase.

A diary was dispensed to all subjects eligible for the actual-use phase of the study and they were shown how to use it. Subjects were asked to provide the following information in the diary each time they used Prilosec1: the date of the dose, the time of the dose, and the number of tablets taken. If subjects returned to purchase additional product, a new diary was issued. Throughout the study period, information was also recorded on concomitant medications, which subjects may have taken (including other heartburn medications); whether there were any adverse experiences; and (for women) the results of the pregnancy tests.

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

End-of-Study Visit (Visit 2)
Subjects had the following procedures performed during this visit:

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

3-Month Follow-up Telephone Questionnaire
Those subjects who completed the actual-use portion of the study (returned a diary), were telephoned by study personnel approximately 3 months after the initial visit. They were asked whether or not they had spoken with a physician, a nurse in a physician's office, a nurse practitioner, or a physician's assistant about their heartburn since their end-of-study visit, and whether they had received any advice or recommendations for heartburn treatment (verbatim responses collected). Subjects were also asked if they had a (future) scheduled appointment with their physician, and if so, whether they planned to discuss their heartburn at that visit. Subjects were also asked if their frequent heartburn returned since stopping the study medication, and, if it did, what they did about it.

Consumer Behavior Endpoints

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

1. The percentage of subjects that correctly self-selected that the study medication was a drug that they could use, and
2. If the subject reported that the medication was one they could use for their heartburn, then they were considered correct if they:

- reported a history of two or more days of heartburn per week or reported taking heartburn medications two or more days per week,
- were at least 18 years of age,
- were not pregnant or nursing,
- were not allergic to omeprazole,
- did not report any alarm symptoms,*
- were not taking any contraindicated medications*

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

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

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

Physician Advice and Supervision

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

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

- a prescription medication for their heartburn (within the past year and/or at any time prior to the study), or
- a scheduled appointment with a physician or supporting healthcare provider to discuss their heartburn.

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

- Consumer Reasons Why Not Appropriate to Use

"I don't get heartburn."
"I don't get heartburn more than once a week."
"I am pregnant or nursing a child."
"I am currently taking a medication I shouldn't take with Prilosec1."
"I have a condition mentioned on the label warning."
"I am under 18 years of age."
"Other."

- Consumer Reasons Why Appropriate to Use

"I get frequent heartburn."
"I want to prevent heartburn."
"I'm familiar with this medication and/or have tried Prilosec."
"Other heartburn medications are not effective enough."
"It has convenient dosing/24-hour duration."
"Other."

Participation Status
Those subjects who self-selected Prilosec1 as a medication they could use for their heartburn were asked if they were willing to participate in the study. Subjects who responded "no" had their reason(s) recorded verbatim. Verbatim responses were classified by the sponsor into response categories after the consumer's self-selection decision had been made. The categories were pre-specified as follows:
"I don't like to try new medications without my physician's approval."
"The product is too expensive."
"I don't use medications or I only use natural remedies."
"Study participation would not be convenient."
"I am happy with my current heartburn medication."
"Other."

Physician Consultation
Subjects may have contacted a physician (study or personal), nurse practitioner, physicians assistant, or nurse in a physician's office prior to enrollment or at anytime during this study. Further, approximately 3 months after the initial visit, all subjects participating in the actual-use phase of the study were to be contacted by telephone to

answer a questionnaire to determine whether or not over the past month they had spoken with a physician, a nurse in a physician's office, a nurse practitioner, or a physician's assistant about their heartburn, and whether they had received any advice or a recommendation for heartburn treatment. The subject was also asked if they had a (future) scheduled appointment with their physician, and if so, whether they planned to discuss their heartburn at that visit.

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

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

Statistical Methods and Analysis Plans

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

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

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

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

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

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

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

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

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

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

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

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

Dosing behaviors, such as total number of dosing days, total number of tablets taken, dosing duration, and maximum and minimum consecutive dosing days were also summarized as frequency distributions in tabular and/or graphical fashion. Subjects who agreed to participate in the study and returned a diary, but decided not to use the study medication, were not included in the analyses/summaries of dosing since no drug usage behavior was available. All subjects who returned their diary had all available data

included in the consumer behavior measures. The diary was the definitive source of data about consumer behavior and study medication usage. A subject was considered "complete" if they returned one or more diaries.

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

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

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

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

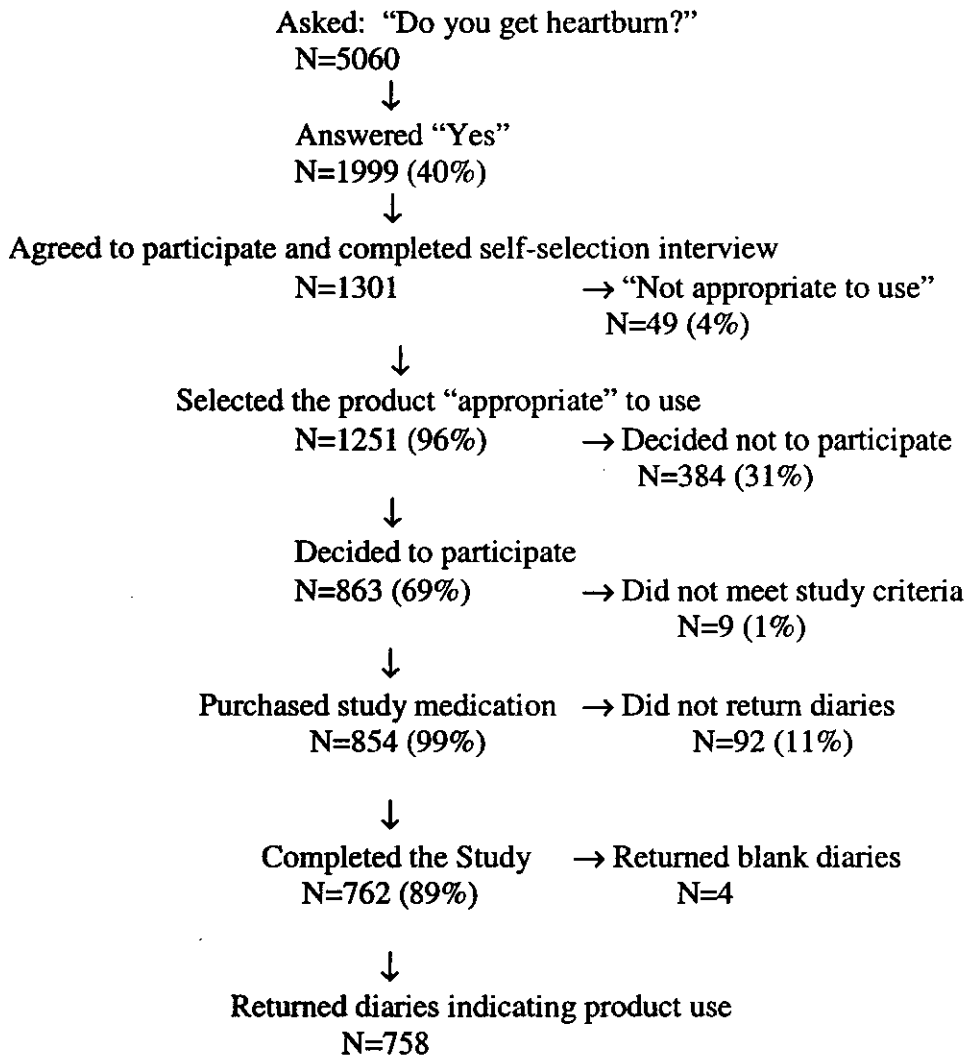
- The percentage of subjects who took no more than one tablet per dose on all doses.
- The percentage of subjects who took no more than one dose and no more than one tablet on all days.

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

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

Results

The following chart displays a disposition of the subjects.



The reasons for 49 subjects who stated that Prilosec1 is not appropriate for them to use are listed below:

- 14 (28.6%) do not get heartburn more than once a week,
- 2 (4.1%) pregnant or nursing a child,
- 12 (24.5%) taking a contraindicated medication,
- 7 (14.3%) had a condition mentioned on the label warning, and
- 14 (28.6%) other reasons.

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

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

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

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

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

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

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

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

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

Data Sets Analyzed/Determination of Product Appropriateness to Use
All subjects who took at least one dose of study medication as indicated in their returned diaries were used in the analyses/summaries of dosing behavior. This included the consumer behavior summaries relative to dosing instructions as well as number of dosing days, tablets taken, etc. Of the 762 subjects who returned one or more diaries, 4 subjects returned blank diaries while 758 returned diaries indicating product usage. Thus, the analyses summarizing behavior related to dosing instructions is based on these 758 subjects.

For the self-selection summaries, the **primary population** (N=770) consisted of those subjects who used study medication (N=758) plus those subjects who did not participate based on study-related criteria (N=12) (i.e., providing consent, underage, pregnant, and previous study participation). The **secondary population** for the self-selection summaries is comprised of all subjects who participated in the self-selection interview

and selected the drug as appropriate to use, whether or not they purchased Prilosec1 (N=1251). The consumer reasons for self-selecting the drug "appropriate" to use were classified by the sponsor into pre-specified non-inclusive response categories. Table 4 shows a distribution of subjects in primary and secondary populations by the reason for self-selection categories:

Table 4. Summary of Consumer Reasons Why Appropriate to Use

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

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

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

The one subject who attempted to enter the trial while pregnant (Subject 020138) was a 34-year-old Black female who is a manager/administrator with a college degree. She had a history of frequent heartburn (4–5 days per week) for greater than 5 years, and had been in contact with her doctor and received a prescription for Prevacid within the past year. She had a history of taking Prilosec, and listed Prevacid and Synthroid as her current medications. She listed one contraindicated condition (sweating, shortness of breath or lightheadedness) for which she had consulted her doctor and received a prescription. She was also currently under evaluation by her doctor for unexplained nausea. When study personnel asked the subject if she was pregnant, she answered 'yes'. This is the first pregnant female that has attempted to enter a use study/take Prilosec1 in the all of the previous use studies, totaling approximately 2000 subjects.

Demographic and Baseline Characteristics

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

Table 5. Demographic Characteristics of Treated and Enrolled Populations

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

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

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

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

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

Of the total treated subjects 449 (59%) were female and 309 (41%) were male, ranging in age from 18 to 91 years with a mean age of 49 years. The majority (70%) of the subjects were Caucasian, 14% were Black, 10% were Hispanic, and 6% made up other races. Of the subjects who dosed, 228 (30%) indicated that their highest education consisted of a high school diploma, GED or below, and 530 (70%) subjects indicated that they had completed at least some college. The REALM test scores revealed that of those subjects that were tested (n=223), 60 were categorized as low literate (scored ≤ 60). In terms of occupations, 29% indicated their occupation was technical or professional, 15% were managers or administrators, 10% were sales workers, and all other occupations occurred at a rate of less than 10%.

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

Heartburn History

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

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

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

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

Prior Therapies

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

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

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

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

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

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

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

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

Concomitant Medications

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

Comments:

Data from the study suggest that it is likely that Prilosec will be used by subjects with contraindicated symptoms. A total of 8.2% (n=62) of the total treated population had those symptoms and selected to use Prilosec1 despite the warnings on the label.

The proposed label states: "Do not use with other acid reducers." The information on the use of concomitant medications is not useful. It does not provide any information who needed to take a back up medication or why. Medications used prior to the enrollment into the study as well as during the study were lumped together. Four out of five previously conducted actual use studies by the sponsor had collected information on concomitant use of other heartburn medications. Data from those studies showed that, in addition to omeprazole, 11-20% of people were taking antacids, 2-19% H2RAs, and up to 3% PPIs.

Self-Selection

The pre-specified primary parameter for determining correctness of self-selection was to meet all 6 individual criteria (i.e., experienced heartburn $\geq$ 2 days/week, were $\geq$ 18 years old, were not pregnant/lactating, were not allergic to omeprazole, had no contraindicated symptoms that were not reported to a healthcare provider, and were not taking any

contraindicated medications without notification to a healthcare provider). Using this definition, 642 (83%) out of 770 subjects in primary population and 961 (76%) out of 1251 subjects in secondary population selected the study medication as "appropriate" to use. Summary of correct self-selection rates by demographics and study centers is presented in Table 9.

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

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

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

Data also show that correct self-selection rates varied when analyzed by race, literacy level, and study center. Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. One study center (Atlanta, GA) had the lowest self-selection rate. The only difference in demographics of the enrolled population at this center was higher percentage of blacks (43%) compared to the other centers (ranged from 1 to 23 %). Literacy level of the participants of the same center was actually higher than that of the other sites. Seventy five (75%) percent of the participant at the center #2 had at least some of the college education compared to the other centers, where subjects with some college education comprised from 57 to 68 %.

Compliance to Dosing Directions and Associated Behaviors

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

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

Compliance with Dosing Directions	N=758 (%)
Compliant with 3 label use directions	478 (63%)
Not compliant with 3 label use directions	280 (27%)
• Exceeded 1 tablet per dose	31 (4%)
• Exceeded 1 dose per day	69 (9%)
• Exceeded 14 consecutive days	23 (3%)

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

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

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

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

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

Table 11. Compliance with Label Use Directions by Subcategories

		Compliance rates
Gender	Female (N=449)	81%
	Male (N=309)	77%
Race	Caucasian (N=530)	82%
	Non-Caucasian (N=228)	72%
Age	< 65 years (N=594)	79%
	≥ 65 years (N=163)	82%
Study Center	Vernon, CT (N=119)	71%
	Atlanta, GA (N=147)	76%
	West Palm, FL (N=192)	82%
	Trumbull, CT (N=158)	77%
	Modesto, CA (N=142)	88%
Literacy Level	REALM ≤60 (N=60)	73%
	REALM >60 (N=693)	80%
History of HB frequency	≤ 1 day/week (N=67)	51%
	2-3 days/week (N=257)	76%
	4-5 days/week (N=107)	85%
	6-7 days/week (N=327)	85%
History of HB duration	≤ 3 months (N=15)	73%
	4-12 months (N=57)	75%
	1-2 years (N=137)	78%
	3-5 years (N=202)	79%
	> 5 years (N=347)	80%

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

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

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

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

When the subjects who took study medication and were available for Visit 2 (N=744) were questioned about why they used Prilosec1 on more than 14 total days (total of 23 subjects), 11 subjects stated it was because they were accustomed to taking heartburn medications that way; 6 subjects stated because a healthcare provider (HCP) had told them to take it that way; 4 stated because they know that prescription Prilosec1 is taken that way; 17 had other reasons. The question was not applicable for subjects who did not exceed 14 days of dosing (95% of the population). Similarly, when subjects were questioned about taking Prilosec1 on fewer than 14 consecutive days, 38 subjects stated it was because they were accustomed to taking heartburn medications that way; 24 subjects stated because they forgot to take it; 3 stated because someone (friend, HCP, etc.) told them to take it that way; 161 had other reasons. The question was not applicable for subjects who did not dose less than 14 consecutive days (72% of the population).

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

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

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

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

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

Comments:
The sponsor did not have a prespecified compliance rate prior to the study initiation. Overall compliance with all three labeled directions in this study was 63%. In five previously conducted Prilosec actual use studies, compliance ranged from 58 to 83%. The highest rate was achieved in the study where subjects were dispensed fewer tablets (12 tablets for a 10 day labeled directions of use). The compliance rate in this study increases significantly (from 63% to 79%), when the sponsor analyzes compliance with the 14-day regimen, by subjects taking between 11 to 14 doses of study medication in an 11-17 day period. It is not clear, why the sponsor included this range of "acceptable" dosing duration.

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

that the history of use of any Rx heartburn medicine somehow justifies non-compliance with the use of Prilosec1.

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

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

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

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

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

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

Doctor/Healthcare Provider Consultation and 3-Month Follow-up Questionnaire
Subjects could contact their healthcare provider at more than one point. Of a total of 758 subjects 119 (16%) contacted their healthcare provider during the 2-month study, 126

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

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

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

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

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

3-month Follow-up Questionnaire (Return of Frequent Heartburn)
Out of a total of 649 who were available for 3-month follow-up 276 (43%) subjects did not have their frequent heartburn return after they stopped taking Prilosec1. Of those who did have their frequent heartburn return (n=373), 171 (46%) subjects took an antacid heartburn medication; 99 (27%) took a prescription heartburn medication; 78 (21%) subjects took an OTC acid reducer; 75 (20%) subjects consulted a healthcare provider; 36 (10%) changed their lifestyle; 29 (8%) did something else; and 22 (6%) did not do anything after their frequent heartburn returned. Subjects' responses could fit into more than one category.

Overall Assessment of Study Medication
Overall, 93% of the study population rated the product as Good, Very Good or Excellent: 48% of subjects rated the study medication Excellent, 34% of subjects rated the study

medication Very Good, 12% of subjects rated the study medication Good, 3% rated the study medication Fair, and 2% of subjects rated the study medication Poor.

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

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

Overall, the correct self-selection rate was 83% for the primary population and 76% for the secondary population. Correct self-selection rates were lower overall in the secondary vs. the primary population. Data also show that correct self-selection rates varied when analyzed by race, literacy level, and study center. Lower correct self-selection rates were seen in non-Caucasians and in the low literacy group. There were a total of 13.5% of self-selection (secondary) and 9% of treated (primary) population that suffered from infrequent heartburn ($\leq$ 1 day a week), and therefore inappropriately self-selected themselves. This shows that Prilosec1 is likely to be used for episodic occasional heartburn. Data from the study also suggest that it is likely that Prilosec will be used by subjects with contraindicated symptoms. A total of 8.2% of the total treated population had those symptoms and selected to use Prilosec1 despite the warnings on the label.

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

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

Conclusions:

1. *One of the major deficiencies of the study is that it did not collect information on the reasons why subjects were taking Prilosec1, for prevention vs. relief or other. The second major deficiency of the study was that information on the consultation with HCP was not confirmed by the study personnel.*
2. *The study was of a short duration and did not address the issues of repeat courses of self-medication, return of the frequent heartburn etc.*
3. *Overall, the correct self-selection rate was 83% for the primary population and 76% for the secondary population.*
4. *The label states: "Notify your doctor if you have had heartburn for 3 months or longer without talking to your doctor". The results of the study show that almost all subjects (98%) who used the drug had heartburn symptoms for more than 3 months, and only half of them (48%) had spoken to their physician within the last year, and 265 (35%) subjects had not spoken to a health care provider at all.*
5. *The data show that Prilosec1 is likely to be used for episodic heartburn. There were total of 9% of subjects of the treated population and 13.5 % of self-selection population with episodic heartburn ($\leq$ 1 day a week), which is an underestimate.*
6. *Data from the study suggest that it is likely that Prilosec will be used by subjects with contraindicated symptoms. A total of 8.2% of the total treated population had those symptoms and selected to use Prilosec1 despite the warnings on the label.*
7. *At the time of enrollment, 265 (35%) subjects out of the total treated population (n=758 stated that they had never spoken to a physician about their heartburn. During the study, 54 out of those 265 subjects did have doctor consultation. The remaining 211 subjects (28% of the total treated population) never had a consultation with a health care provider.*
8. *Overall compliance with all three labeled use directions (take 1 tablet a day, every day for 14 days) in this study was 63%. The compliance rate in this study increases significantly (from 63% to 79%), when the sponsor analyzes compliance with the 14-*

day regimen, by subjects taking between 11 to 14 doses of study medication in an 11-17 day period.

9. *The responses to the follow-up questionnaire showed that more than half (58%) of the subjects available for follow-up had their heartburn return, and only 20% of those contacted their health care provider.*

VII. Integrated Review of Safety

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

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

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

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

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

A total of 759 subjects were exposed to Ome-Mg 20 under actual use conditions. The extent of exposure for the 758 study participants is displayed in Table 13. A total of 37 subjects (4.8%) took more than 14 tablets; 19 subjects took between 15 and 28 tablets; and 18 subjects took between 29 and 56 tablets. Note, 2 subjects (030267 and 020234) are included in these numbers as having taken 18 and 15 tablets, respectively, because that is what was reported in their diary; however, each subject only purchased one carton (14 tablets) of study medication. Additionally, 56 subjects took a total of 10 tablets or less.

Table 13. Summary of Extent of Exposure

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

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

Table 14. Summary of Adverse Events

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

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

Table 15. Adverse Events by Body System

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

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

Table 16. Most Common Adverse Events by COSTART Term

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

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

Deaths

No deaths were reported in this study.

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

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

Other Significant Adverse Events
There were no other significant AEs reported in this trial.

Discontinuation Due to Adverse Events
Three subjects had AEs that resulted in discontinuation from the study.

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

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

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

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

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

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

Vital Signs, Physical Findings, and Other Safety Observations
No vital signs or physical examinations were performed in this study.

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

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

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

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

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

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

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

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

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

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

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

Case # 2000AH00903. A 70-year-old male smoker with a history of chronic obstructive pulmonary disease and decompensated heart failure was hospitalized due to vomiting blood (2-3 days), dyspnea, and progressive weight loss. Concomitant medications included theophylline, amphotericin B, amiodarone hydrochloride, furosemide/spironolactone, isopromethazine hydrochloride, tramadol hydrochloride, budesonide and formoterol. He was treated with an infusion of omeprazole; the dyspnea continued overnight. The next day an esophago-gastro-duodenoscopy was performed which showed an axial hernia, second-degree reflux esophagitis with signs of bleeding and candida esophagitis. Treatment with amiodarone hydrochloride was maintained and omeprazole magnesium 20 mg daily was added. The next morning, the patient was transferred to the intensive care unit with suspected acute liver failure. The patient died

three days later after developing acute liver failure, anuria and worsening cardiopulmonary parameters. The cause of death was reported as cardiovascular arrest due to biventricular heart failure with disseminated infarct-like lesions and extensive centrolobular liver failure. Autopsy showed heart and liver failure were of ischemic origin due to myocarditis. The reporting physician made no assessment of causality.

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

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

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

Non-Serious Post-Marketing Adverse Events

A total of 430 non-serious adverse events were reported among 257 patients for omeprazole magnesium MUPS tablets worldwide during the reporting period from January 1, 2000 through June 30, 2001. The five most common AEs reported were drug ineffective, dyspepsia, dermatitis nos, abdominal pain nos and nausea. All of the reported adverse events are currently listed on Prilosec prescription label.

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

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

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

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

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

Additional adverse experiences listed on the current prescription label, occurring in < 1% of patients or subjects in domestic and/or international trials, or occurring since the drug was marketed, are shown below for each body system. In many instances, the relationship to PRILOSEC was unclear.
Body as a Whole: Allergic reactions, including, rarely, anaphylaxis, fever, pain, fatigue, malaise, abdominal swelling.
Cardiovascular: Chest pain or angina, tachycardia, bradycardia, palpitation, elevated blood pressure, peripheral edema.
Gastrointestinal: Pancreatitis (some fatal), anorexia, irritable colon, flatulence, fecal discoloration, esophageal candidiasis, mucosal atrophy of the tongue, dry mouth. During treatment with omeprazole, gastric fundic gland polyps have been noted rarely. These polyps are benign and appear to be reversible when treatment is discontinued. Gastro-

duodenal carcinoids have been reported in patients with ZE syndrome on long-term treatment with PRILOSEC. This finding is believed to be a manifestation of the underlying condition, which is known to be associated with such tumors.
Hepatic: Mild and, rarely, marked elevations of liver function tests [ALT (SGPT), AST (SGOT), (gamma)-glutamyl transpeptidase, alkaline phosphatase, and bilirubin (jaundice)]. In rare instances, overt liver disease has occurred, including hepatocellular, cholestatic, or mixed hepatitis, liver necrosis (some fatal), hepatic failure (some fatal), and hepatic encephalopathy.
Metabolic/Nutritional: Hyponatremia, hypoglycemia, weight gain.
Musculoskeletal: Muscle cramps, myalgia, muscle weakness, joint pain, leg pain.
Nervous System/Psychiatric: Psychic disturbances including depression, aggression, hallucinations, confusion, insomnia, nervousness, tremors, apathy, somnolence, anxiety, dream abnormalities; vertigo; paresthesia; hemifacial dysesthesia.
Respiratory: Epistaxis, pharyngeal pain.
Skin: Rash and, rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme; purpura and/or petechiae (some with rechallenge); skin inflammation, urticaria, angioedema, pruritus, alopecia, dry skin, hyperhidrosis.
Special Senses: Tinnitus, taste perversion.
Urogenital: Interstitial nephritis (some with positive rechallenge), urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, gynecomastia.
Hematologic: Rare instances of pancytopenia, agranulocytosis (some fatal), thrombocytopenia, neutropenia, anemia, leucocytosis, and hemolytic anemia have been reported.

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

VIII. Dosing, Regimen, and Administration Issues

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

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

Uses
•for **prevention** of the symptoms of frequent heartburn for 24 hours

•only for those who suffer heartburn two or more days a week

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

Do not use
•with other acid reducers

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

Ask a doctor of pharmacist before use if you are taking
•warfarin (blood thinning medicine)
•phenytoin (seizure medicine)
•ketoconazole (prescription antifungal medicine)

Stop use and ask a doctor if
•stomach pain continues or worsens
•heartburn continues or returns after using this product everyday for 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of the reach of children. In case of overdose, get medical help or contact a Poison Control center right away.

Directions
Adults 18 years of age or older
•for prevention of frequent heartburn, swallow 1 tablet with a glass of water in the morning
•take every day for 14 days
•do not continue beyond 14 days unless directed by your doctor. If your frequent heartburn continues or returns, it could be a sign of a more serious condition.
•do not take more than 1 tablet a day
•do not chew or crush the tablets
Children under 18 years of age: as a doctor

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

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

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

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

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

IX. Use in Special Populations

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

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

X. Conclusions

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

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

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

Concurrence:

Appendix 1.

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

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

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

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

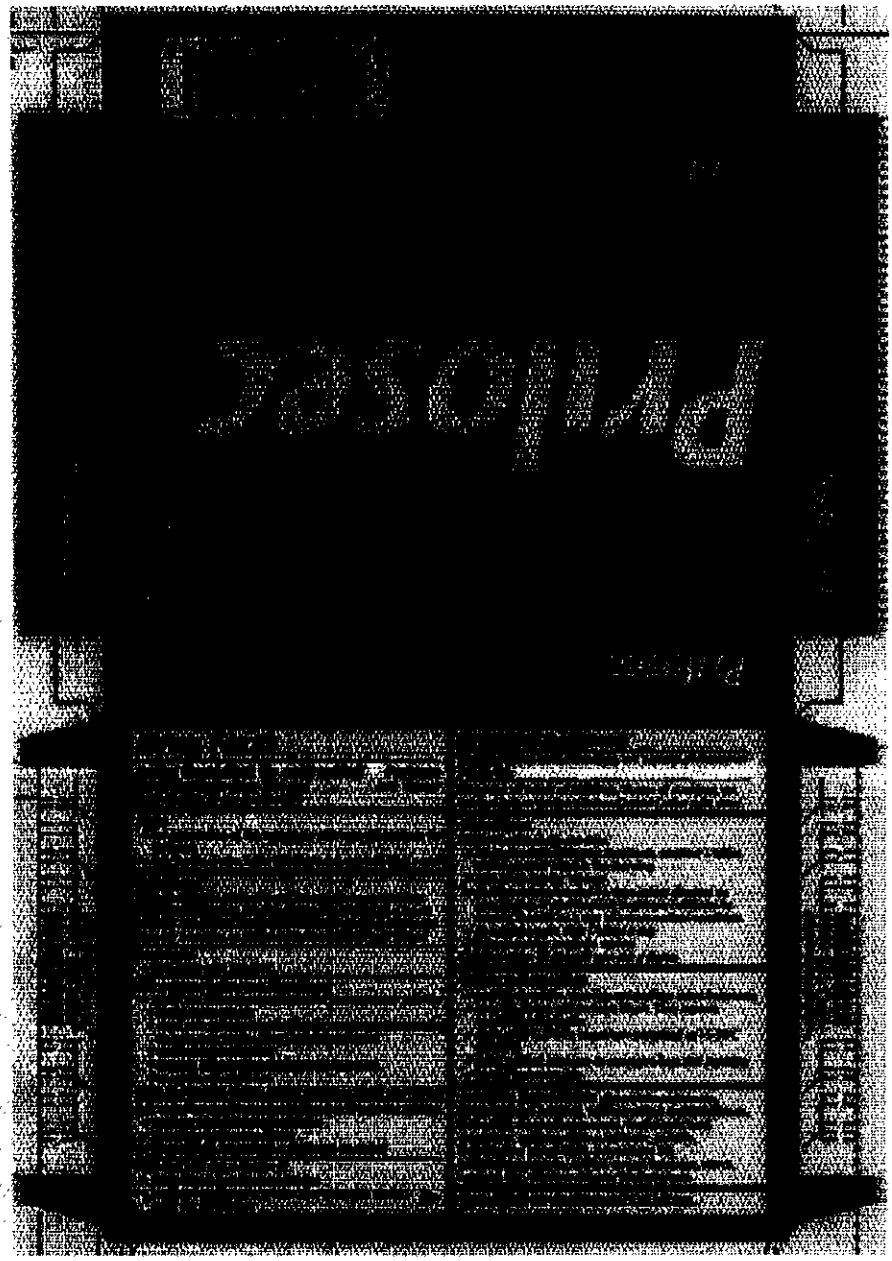
	Non-Serious N=430 (%)*	Serious AEs N=109 (%)**
Weight increased	1 (0.2)	0 (0.0)
Hepatic function abnormal nos	0 (0.0)	4 (3.7)
Stevens Johnson syndrome	0 (0.0)	3 (2.8)
Toxic epidermal necrolysis	0 (0.0)	3 (2.8)
Anaphylactic reaction	0 (0.0)	2 (1.8)
Erythema nec	0 (0.0)	2 (1.8)
Hematemesis	0 (0.0)	2 (1.8)
Hepatitis cholestatic	0 (0.0)	2 (1.8)
Hepatitis nos	0 (0.0)	2 (1.8)
Hepatocellular damage	0 (0.0)	2 (1.8)
Aggression	0 (0.0)	1 (0.9)
Anaphylactic shock	0 (0.0)	1 (0.9)
Anxiety	0 (0.0)	1 (0.9)
Atrial fibrillation	0 (0.0)	1 (0.9)
Balance impaired	0 (0.0)	1 (0.9)
Blood sodium increased	0 (0.0)	1 (0.9)
Bone marrow depression nos	0 (0.0)	1 (0.9)
Completed suicide	0 (0.0)	1 (0.9)
Crying	0 (0.0)	1 (0.9)
Delirium	0 (0.0)	1 (0.9)
Depression aggravated	0 (0.0)	1 (0.9)
Depression nec	0 (0.0)	1 (0.9)
Electrocardiogram abnormal nos	0 (0.0)	1 (0.9)
Epilepsy nos	0 (0.0)	1 (0.9)
Gastrointestinal hemorrhage nos	0 (0.0)	1 (0.9)
Hepatic failure	0 (0.0)	1 (0.9)
Hepatic fibrosis	0 (0.0)	1 (0.9)
Leucopenia nos	0 (0.0)	1 (0.9)
Esophagitis nos	0 (0.0)	1 (0.9)
Pancreatitis nos	0 (0.0)	1 (0.9)
Peripheral swelling	0 (0.0)	1 (0.9)
Petit mal epilepsy	0 (0.0)	1 (0.9)
Polyarthralgia	0 (0.0)	1 (0.9)
Proctalgia	0 (0.0)	1 (0.9)
Pulmonary fibrosis	0 (0.0)	1 (0.9)
Rigors	0 (0.0)	1 (0.9)
Sore throat nos	0 (0.0)	1 (0.9)
Speech disorder nec	0 (0.0)	1 (0.9)
Suicide attempt	0 (0.0)	1 (0.9)
Syncope	0 (0.0)	1 (0.9)
Tachycardia nos	0 (0.0)	1 (0.9)
Thyroid disorder nos	0 (0.0)	1 (0.9)
Thyroid nodule	0 (0.0)	1 (0.9)

* Percentage of total non-serious adverse events reported

** Percentage of total serious adverse events reported

Appendix 2.

Label Proposed for the OTC Marketing.



NDA:	**21-229**
Product:	**Prilosec (omeprazole magnesium tablets 29 mg)**
Sponsor:	**Astra Zeneca/Proctor & Gamble**
Indication:	**Relief and prevention of heartburn**
Marketing:	**OTC**
Submission:	**Safety Update**
Date Submitted:	**Jan, 2000, May, 2000**
Date Received:	**May, 2000**
Date Reviewed:	**August, 2000**
Medical Reviewer:	**Ling Chin, M.D., M.P.H.**

I. INTRODUCTION

Omeprazole was first marketed for clinical use in Europe in 1988, and in the United States (U.S.) in 1989. Since that time, approximately 300 million courses of patient treatments have been prescribed worldwide in 103 countries for various acid-related gastrointestinal disorders, with 90 million courses in the U.S. See Appendix 1.

Omeprazole has been marketed under the trade name LOSEC in Europe and under the trade name PRILOSEC in the United States. Both PRILOSEC and LOSEC are capsules. Omeprazole magnesium (Ome-Mg), the magnesium salt of omeprazole, a tablet, was selected for clinical development for over-the-counter (OTC) use. Results of bridging studies to compare Ome-Mg and omeprazole indicate that their toxicokinetic and toxicological profile are equivalent. Pharmacokinetic studies have demonstrated relative bioavailability between omeprazole capsule and Ome-Mg tablet formulations.

Ome-Mg is approved for prescription use in 26 countries. See Appendix 2. It is available under the trade names of LOSEC, LOSEC tablets, and LOSEC MUPS, since February of 1998. MUPS (multiple unit pellet system) is a disintegrating tablet containing enteric-coated pellets. Ome-Mg is available in Canada as a delayed release (enteric-coated) tablet, which is a different formulation than the MUPS formulation. Ome-Mg is approved for OTC use only in Sweden, available as LOSEC MUPS since 2/1998. Ome-Mg MUPS has never been marketed in the U.S. and is the proposed formulation for OTC marketing.

This is a review of the global post-marketing experience of the Delayed Release and MUPS tablet formulations. The global post-marketing experience of omeprazole capsules will be reviewed by reviewers from the GI division. Safety information from all the OTC trials will be reviewed separately in each individual clinical and actual use study review, and will not be included here.

II. OMEPRAZOLE-MAGNESIUM MUPS TABLET WORLDWIDE POST-MARKETING ADVERSE EVENTS

The safety update included adverse event (AE) reports received by Astra Zeneca (Sweden) since first launch of the MUPS tablet formulation in February 1998 up to December 31, 1999, from all countries where the tablet formulation is marketed. All AE reports associated with omeprazole magnesium MUPS irrespective of indication or causality assessment are included in this summary. This includes reports with very limited information (e.g., inquiries from doctors and pharmacists), provided they contain minimum information required for a report, i.e., an identifiable patient, source, drug and adverse reaction. Consumer reports received during the period are included. The AEs are presented according to the AstraZeneca Adverse Event Dictionary, a modified version of WHOART.

There were a total of 11.6 million patient treatment courses of Ome-Mg distributed to wholesalers during 2/98 to 12/99. There were a total of 219 cases, reporting 398 adverse events. A case represents a single patient who may have more than one adverse event occurring within one or more body systems.

Table 1: Adverse Events reported for MUPS by Body System (2/98-12/99)

Body System	Number Cases	Serious		Non-Serious
		Fatal	Non-Fatal	
Skin and Appendages	35		4	31
Musculo-Skeletal	9			9
CNS and PNS	25		1	24
Vision	8			8
Hearing, Vestibular	1		1	
Special Senses	4			4
Psychiatric	10		3	7
Gastrointestinal	103		5	98
Liver Biliary	6	1	4	1
Metabolic Nutritional	6		1	5
Endocrine	1			1
Cardiovascular, General	2		2	
Myo Endo Pericardial Valvular	1	1		
Heart Rate, Rhythm	2		1	1
Vascular	2		1	
Respiratory	3		1	2
Red Blood Cell Disorders	3		2	1
White Cell and RES Disorders	1		1	
Platelet, Bleeding and Clotting	3		1	2
Urinary	5		2	3
Reproductive	3			3
Body as a Whole	82		7	75
Resistance Mechanism	1		1	
Total Cases*	219	2	25	192
Total AEs*	398	2	44	352

* A single patient is counted as 1 case. However, a single case may have more than one adverse event occurring within one or more body systems. Therefore the numbers of AEs do not coincide with the total number of cases.

Fatal Serious Adverse Events:
There are 2 fatal cases out of a total of 27 serious cases in the reporting period specified. The fatal cases are summarized below:

Case 3991832:
74 y.o. woman with a history of hypertonia and hysterectomy had participated in a clinical study where omeprazole was given as a non-study drug. Three weeks after orthopedic surgery, patient experienced fever, vomiting and pain in the operated knee. She was admitted to the orthopedic unit and transferred to the infectious disease unit for presumptive pneumonia. Omeprazole was given for gastritis. Patient deteriorated, and eventually developed cardiogenic shock and died. Autopsy diagnosis ruled out a myocardial infarct and myocarditis was suspected. The investigator felt that at least 8 drugs were possibly related to the event: omeprazole magnesium, warfarin, cefuroxime, tramadol HCl, erythromycin, cefotaxime, dextropropoxyphene napsilate, and Citodon (codeine and paracetamol).

Case 3992554:
84 y.o. woman treated with omeprazole 80 mg daily for duodenal ulcers. Patient had a history of atrial fibrillation, Type II diabetes and chronic renal insufficiency. Patient was admitted for persistent upper abdominal pain following diagnosis of duodenal ulcer via gastroduodenoscopy. Medications on admission were nitrazepam, Inhibin (hydroquinone, thiamine), domperidone, paracetamol and omeprazole. Several days later, there was a slight deterioration in kidney function with increasing hyponatremia and increasing hyperkalemia. There was a marked increase in LDH level, with considerable increases in the other liver enzymes as well (not noted on admission). Omeprazole was

discontinued and sodium supplements given. A day later, patient died in her sleep. Clinical cause of death was stated as "possibly cardiac due to progressive liver failure, alternatively as a consequence of the medication administered for the recent duodenal ulcer caused by a NSAID."

Medical Officer Comments:
These two fatal cases occurred in elderly women, both of whom were taking several medications concomitantly with omeprazole. In one, omeprazole was given for gastritis, and in the other for duodenal ulcer. In the case of the 74 y.o. woman, her demise occurred in the setting of a serious infection which did not seem responsive to several antibiotics. Death resulted from cardiogenic shock, and there is insufficient information to link omeprazole as the causal agent in this fatality. The 84 y.o. woman who presented with multiple medical problems including chronic renal insufficiency received omeprazole for duodenal ulcers. Omeprazole has been noted to cause elevations in liver enzymes. Rare occurrences of overt liver disease, including some fatal liver necrosis, and hepatic failure is identified in current prescription labeling. Urogenital, including renal, AEs are also listed in prescription labeling. It is known that up to 80% of a dose of omeprazole is excreted renally. Thus, in an elderly woman with multiple medical conditions, including chronic renal insufficiency, the possibility exists that omeprazole may have contributed to the overall demise in this patient. However, there is not enough information to definitively establish omeprazole as the causative agent.

Non-Fatal Serious Adverse Events (SAE):
There were 25 cases of SAEs, which did not result in death, reporting a total of 44 AEs. The sponsor has provided summary tables for the distribution of these cases by body system and WHOART term.

Table 2: SAEs in Most Frequently Occurring Body Systems (Top 4)

Body System	Number Cases	Serious Non-Fatal
Body as a Whole	103	7
Gastrointestinal	82	5
Skin and Appendages	35	4
Liver Biliary	6	4
Hematologic*		4*
Psychiatric	10	3
Urinary	5	2
Red Blood Cell Disorders*	3	2
Cardiovascular, General	2	2

* Sponsor had the hematologic disorders grouped under several body systems such as red blood cell disorders, white cell and reticuloendothelial (RES) system disorders, and platelet, bleeding and clotting disorders. If these AEs were generally grouped under the Hematologic body system, a total of 4 cases would have resulted, and would have placed it in one of the top 5 most frequently occurring body system with reported AEs.

By specific terms, the AEs occurring in the top 5 most frequently occurring body system are as follows:
(1) Body as a Whole: allergic reaction, anaphylactic shock, lack of efficacy, fever, oedema, oedema legs, retrosternal pain, swelling legs
(2) Gastrointestinal: abdominal discomfort, diarrhoea, gastritis, GI haemorrhage, nausea, pancreatitis, stomach pain
(3) Skin and Appendages: angioneurotic edema, exanthema, rash maculo-papular, toxic epidermal necrolysis
(4) Liver Biliary: bilirubinaemia, cholelithiasis, cholestasis intrahepatic, hepatic enzymes increased, hepatic failure (fatal)
(5) Hematologic: pancytopenia, agranulocytosis, purpura thrombocytopenic

Some cases indicative for the specific adverse event within the most frequently occurring body systems are presented below.

Case #19991100368:
65 y.o. female with history of multiple drug sensitivities, was switched to LOSEC MUPS and experienced an allergic reaction characterized by wheezing, and throat swelling, requiring hospital treatment. Previously she was taking LOSEC capsules 10 mg (sometimes 20 mg) QD. Follow-up information stated that she started MUPS on 10/29/99 and her legs began to swell. The next day, she experienced breathing difficulty, and rapid heartbeat with worsening of her leg swelling. She was treated in the ER with parenteral diuretics and discharged on oral diuretics. Omeprazole capsules continued to be taken 11/1 to 11/3, and she experienced leg swelling and breathlessness again. Omeprazole MUPS was discontinued and lansoprazole was initiated with resolution of adverse events. The doctor described the events as oedema to knees and possible left ventricular failure. Allergic reaction was added as an adverse event.

Case #19991100532:
57 y.o. with history of anaphylactic reaction to penicillin, was started on omeprazole 20 mg daily for gastric ulcer disease. One and a half hours after treatment, she experienced anaphylactic shock with urticaria, angioneurotic oedema, and severe bronchospasm. She improved with IV promethazine HCL, IV methylprednisolone+sodium succinate, oxygen, nebulized ipratropium bromide+albutamol sulfate, and was dishcarged 2 hours later on betamethasone and chlorpheniramine..

Case #19991100300:
Male patient with a history of GI bleed switched was switched from LOSEC Capsules (X 4 years) to LOSEC MUPS for about a month. Developed gastritis and gastric discomfort one week after initiating treatment with LOSEC MUPS, and was admitted for GI bleed. Patient commented that LOSEC MUPS was like "taking no treatment at all." Follow up information stated that patient recovered after LOSEC MUPS was stopped and started back on LOSEC capsules.

Case #20000300045:
70 y.o. male patient experienced abdominal pain (retrosternal pain per physician) 4 days after initiating therapy with MUPS 10 mg daily for oesophagitis, Barrett's oesophagus, and peptic ulcer treatment. Event resolved 7 days later when MUPS was stopped, and within 4 hours of initiation with LOSEC capsules. Patient has been treated with LOSEC capsules since '94 without problems.

Case #19991000268:
67 y.o. woman started omeprazole MUPS 10 mg daily and experienced diarrhoea 4 hours later. Diarrhoea continued after intake of MUPS over the next 2 days. Diarrhoea resolved when MUPS was stopped. Switched to omeprazole capsules without problems.

Case #19981200264:
80 y.o. woman with multiple medical problems including longstanding heart and stomach problems, on multiple medications, had been treated with omeprazole capsules 20 mg daily for gastritis. In 11/98, after being switched to omeprazole magnesium tablets, she experienced stomach pain and nausea which required hospitalization for 2-3 days. Omeprazole magnesium was stopped and symtpoms were resolving at time of report.

Case #19991200396:
47 y.o. male with H. pylori-positive reflux oesohagitis, gastritis, and duodenitis was placed on long-term therapy with omeprazole MUPS tablets 20 mg daily. Patient developed gallstones (duration of use not specified) and had increased liver enzymes (ASAT, ALAT, γ-GT, AP) and biliary pancreatitis (highly increased lipase). Patient was hospitalized, omeprazole magnesium was stopped, and had a gallbladder operation. Liver enzymes were not normalized at time of report.

Case #19990800326:
42 y.o. woman was started on omeprazole magnesium 20 mg daily for dyspepsia. After 4 days, she experienced pruritus. Her GP stopped omeprazole and started lansoprazole the next day, along with cetrizine. Hepatic lab values were increased. Her symtpoms deteriorated and 3 days later, she was hospitalized and lansoprazole was stopped. She had icterus, pruritus, dark urine, pale and loose faeces on admission. Ultrasound showed 2 gallstones without bile duct dilatation or cholesystitis. She was given

Vitamin K. One month later she had a liver biopsy which showed intrahepatic cholestasis, which resolved about 3 months later.

Case #19990300019:
42 y.o. woman with goitre and previous cerebral embolism, was started on omeprazole 10 mg daily for reflux oesophagitis. 3 days later, she experienced restlessness, warm skin, increased blood pressure, tachycardia, inreased weight and thirst, dypsnoea, oedema in her legs, and increase in hepatic enzymes. A week later, patient reported reflux oesophagitis symtoms had receeded. 2 days after that, she had drunk up to 9 L and had a weight gain of 4 kg. Omeprazole was stopped about 2 weeks after starting it. Symptoms of thirst, restlessness, and fluid retention were resolving over the next few days, with most symptoms resolving by day of report another 2 weeks later, except for the thirst increase. Concomitant meds: procoumon, levothyroxine sodium.

Case #19990800731: (Sweden)
77 y.o. female previously treated with omeprazole MUPS tablets for 15 days for non-specific gastric disorder, was treated again a month later, with omeprazole 20 mg daily for vomiting. She was also taking paracetamol. The next day, she developed fever, deteriorated general condition and yellow eyes. She was referred to a clinic 3 days later, where the events were assessed as an adverse reaction and both medications were stopped. Patient recovered. Labs noted for low white and neutrophilic counts and high bilirubin.

Case #19990800557:
69 y.o. man with hypertension, complex partial epilepsy, was admitted for seizures 4/25/99 and presumptive cerebral bleed. Treated with phenytoin and diazepam. Upper trunk exanthema appeared 5/6; phenytoin was suspected and stopped. Valproate started same day. Omeprazole MUPS tablets 20 mg daily also started that day for epigastralgia. Other concomitant meds: haloperidol, furosemide, norfloxacin, paracetamol, amlodipine besilate, citalopram hydrobromide. Patient had fever the next day. 5/10, leukopenia and thrombocytopenia were noted. 2 days later, maculopapular rash appeared on upper arms, then lower legs. Omeprazole stopped 5/11. 5/18 agranulocytosis noted. At time of report (8/3), fever, rash, and thrombocytopenia resolved, but agranulocytosis and leukopenia were still present. Omeprazole assessed as possible causal factor.

Case #19991100494:
22 y.o. woman was treated with omeprazole MUPS tablets 40 mg QD for 10 days for gastritis, in early 10/99. On 11/7, she was admitted for a massive GI bleed with thrombocyte value 3/ul. Patient had been experiencing nosebleeding, hematomas on arms and calves and a prolonged menstruation. Concomitant med: diclofenac for dysmenorrhoea. Physical and lab findings significant for petechiae and hematomas on upper, lower extremities, and both mammae, leukocytes 14.2, Hb 10.8, thrombocytes 11G/L, and mild splenomegaly on ultrasound. Bone marrow cytology showed increased megakaryopoiesis consistent with ITP, and no indication of non-Hodgkin's lymphoma. Over 2 weeks, varying doses of systemic prednisolone and immunoglobulins were given, titrated to improving the thrombocyte count which increased to as much as 259 G/L and fell as much as 8 G/L. Pneumococci vaccine and H. flu vaccine were administered and splenectomy was considered. At the time of the report (12/14/99), there was no further information on resolution of events.

Case #19991200423:
Female patient treated with omeprazole, developed pancytopenia and was hospitalized. Concomitant med: metronidazole, fluconazole.

Case #19990900097:
76 y.o. woman with multiple medical conditions (including drug allergies to bactrim, voltaren, and penicillin with shock symptoms) on multiple meds including omeprazole magnesium. Hospitalised 2/99 for syncope associated with drug abuse, and 3/14/99 for reactive depression. On 3/15, patient had fever and a UTI. Over the next 3 days, she developed exanthema, integumental blisters and erosions of oral mucosa and lips, and severe conjunctivitis, noted to be Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TENS) transitional form. The events were considered life-threatening. Patient recovered 4/15/99. Most

suspected drug was Bactrim, but also considered were: lorazepam, lisinopril-HCTZ, tramadol HCl, as well as omeprazole. The UTI and renal insufficiency were also considered as possible causes.

Case #19990300433:
83 y.o. man, previously on omeprazole capsules, was started on omeprazole MUPS tablets for GI angiodysplasias. After 1 hour, he developed angioneurotic edema of the tongue, with subtotal airway obstruction. Treated with histamine antagonists and corticoids and was intubated. Complete regression of oedema in 36 hours. Multiple medical history including cardiac and cardiovascular problems, and renal insufficiency with retention, on multiple medications. Suspected drugs: omeprazole magnesium, allopurinol, HCTZ-enalapril.

Medical Officer's Comments:
These serious AEs were already noted in the prescription labeling, and during the OTC development, specific adverse events of particular concern were to be addressed by the sponsor. These Special Considerations will be reviewed by medical reviewers from the Gastrointestinal and Coagulation Drug Products Review Division.

Non-Serious Adverse Events:
There were a total of 192 cases, reporting a total of 352 AEs, which were non-serious. Table 3 provides a listing of the top 4 Body Systems which has the most AEs.

Table 3: Non-Serious AEs in Most Frequently Occurring Body Systems (Top 4)

Body System	Number Cases	Non-Serious
Gastrointestinal	103	98
Body as a Whole	82	75
Skin and Appendages	35	31
CNS and PNS	25	24

There was no description of the non-serious AEs except for a listing by specific terms. By specific terms, the AEs occurring in the top 4 most frequently occurring body system are as follows:
(1) Gastrointestinal: abdominal discomfort, abdominal pain, abdominal pain upper, acid regurgitation, a belching, bloating, borborygmus, constipation, cramp abdominal, diarrhoea, dyspepsia, dysphagia, epigastric burning, epigastric pain, eructation, faeces discoloured, feeling sick, flatulence, fullness abdominal, gastric pain, gastritis, gastroesophageal reflux, GI symptoms not otherwise specified (NOS), GI tract bleed NOS, heartburn, hyperacidity, indigestion, liver tender, meteorism, mouth disorder, mouth dry, nausea, oral mucosa burning, reflux oesophagitis, stomach burning, stomach cramps, stomach dilatation, stomach pain, stools lose, tongue burning, vomiting, xerostomia
(2) Body as a Whole: abdominal distention, allergic reaction, back pain, lack of efficacy, fatigue, fever, foot oedema, malaise, oedema arm, oedema legs, pain kidney region, pyrexia, swelling inflammatory localized, swollen abdomen, swollen feeling, therapeutic response decreased, tiredness
(3) Skin and Appendages: angioedema, eczema, erythema, exanthema, hair loss, itching, itching localized, itching rash, pruritus, rash, rash arms, rash generalized, rash localized, skin disorder, skin irritation, skin reaction NOS, sweating, sweating increased, swollen lips, urticaria, vesiculobullous rash, arthralgia, arthritis, joint pain, muscle ache, muscle pain, muscle weakness, myalgia
(4) CNS and PNS: balance difficulty, dizziness, headache, paresthesia, paresthesia legs, tenderness behind eyes, tubular vision, twitching eye

Medical Officer's Comments:
Much of the non-serious AEs by specific terms within each body system reported in the MUPS update was also described in the prescription labeling, either from clinical trial data or postmarketing experience, as listed below.
(1) In U.S. clinical trials (≥1% occurrence): headache, diarrhea, abdominal pain, nausea, URI, dizziness, vomiting, rash, constipation, cough, asthenia, back pain.

(2) In international trials (≥ 1% occurrence): abdominal pain, asthenia, constipation, diarrhea, flatulence, nausea, vomiting, acid regurgitation, headache.
(3) In trials and postmarketing experience (<1% occurrence): AEs from the following body systems were reported: Body as a Whole, Cardiovascular, Gastrointestinal, Hepatic, Metabolic/Nutritional, Musculoskeletal, Nervous System/Psychiatric, Respiratory, Skin, Special Senses, Urogenital, and Hematologic. Fatal cases were noted with pancreatitis, liver necrosis, hepatic failure, toxic epidermal necrolysis, and agranulocytosis.

However, the prescription labeling did not include mention of visual disturbances or eye-related events, which totaled 8 non-serious cases (11.6 million treatments over 2 years) in the MUPS safety update. Overall, the AEs noted to occur with greater frequency were known events.

III. OMEPRAZOLE-MAGNESIUM ENTERIC-COATED TABLET CANADIAN POST-MARKETING ADVERSE EVENTS

A formulation of omeprazole-magnesium tablets different from MUPS was approved in Canada in January 1996 and launched in February 1996. This formulation was called the LOSEC Delayed Release Tablet. See Table 4. A total of 6.4 million treatments were delivered to wholesalers in Canada in that time period. A patient treatment course is counted as one treatment, with the duration of treatment course being 14 or 28 days.

Table 4: LOSEC Delayed Release Tablets in Canada

	First Reporting Period Up to 1/97	Second Reporting Period 2/97-1/98
Treatments	2.7 million	3.7 million
Total Reports	1397	257
Reporting Frequency	0.05% (1 per 2000)	0.007% (1 per 14000)
Total AEs	2335	394
Total SAEs	4	

In the first reporting period, a reporting frequency of 0.05% was observed (one report per 2000 patient treatments). In the second reporting period, the reporting frequency was 0.007% (one report per 14000 treatments). The 4 serious cases in the first reporting period were: 2 cases of angioedema, one case of stomach pain, and one case for lack of efficacy. Table 5 lists the AE reports in the most frequently occurring system organ class for omeprazole capsules and delayed release tablets.

Table 5: Number and (%) AE Reports occurring in most common System Organ Class

System Organ Class	LOSEC Delayed Release Tablets	LOSEC Delayed Release Tablets	Omeprazole Capsules
	Up to 1/97	2/97-1/98	Up to 1/98
GI	914 (65%)	89 (35%)	1601 (20%)
Body as a Whole	744 (53%)	100 (39%)	1342 (16%)
Skin & Appendages	65 (5%)	39 (15%)	1817 (22%)
CNS, PNS	68 (5%)	33 (13%)	1275 (16%)
Psychiatric	20 (1%)	15 (6%)	955 (12%)
Respiratory	16 (1%)	10 (4%)	266 (3%)
Musculoskeletal	13 (1%)	5 (2%)	551 (7%)
Metabolic & Nutritional	4 (0.3%)	9 (4%)	459 (6%)
Liver & Biliary	3 (0.2%)	3 (1%)	400 (5%)
Vision	3 (0.2%)	4 (2%)	294 (4%)
Hematologic*	0 (0%)	1 (0.4%)	568 (7%)
Cardiac & Cardiovascular (all)**	7 (0.5%)	12 (5%)	416 (7%)

* AEs in Red Blood Cell disorders, White Cell and RES disorders, Platelet, Bleeding & Clotting disorders were considered together in Hematologic body system rather than separately.
** AEs in Cardiovascular disorders general, Myo Endo, Pericardial & Valve disorders, Heart Rate & Rhythm disorders, Vascular disorders extracardiac were considered together as Cardiac, Cardiovascular (all) body system rather than separately.

Sponsor noted that the striking difference between LOSEC Delayed Release tablets and Omeprazole Capsules in the first reporting period was due to a greater clustering of events to the GI and Body as a Whole system organ classes with LOSEC tablets. By the second reporting period, the total numbers of AEs had decreased (from 1397 to 237), with the decrease occurring mainly in the GI and Body as a Whole systems. The sponsor attributed this to a decrease of reports of symptoms such as heartburn, nausea, vomiting, and lack of efficacy. The sponsor concluded that, apart from the remaining overrepresentation of reflux symptoms and AEs coded as lack of efficacy, there is no major difference in the adverse event pattern as compared to that of omeprazole capsules.

Medical Officer Comments:
The data reflects the overwhelming clustering of AEs to the GI and Body as a Whole systems in the first reporting period, without an apparent reason. In the first reporting period, within the GI body system, almost all of the reaction descriptions were of symptoms which could reflect the condition for which omeprazole is being used for, such as, heartburn (455 mentions), abdominal pain/discomfort/stomach pain/stomach upset, dyspepsia/epigastric burning, acid indigestion/indigestion, oesophageal burn/discomfort/reflux oesophagitis (149 mentions). Within Body as a Whole, 90% of the mentions were for lack of efficacy (677 mentions). Overall, however, the omeprazole capsule and MUPS tablets experience have continued to show that the top 2 most frequent body systems where the most number of AEs have occurred have been in GI and Body as a whole categories. Therefore, this trend is consistent.

The 4 serious cases in the first reporting period included 2 cases of angioedema, one case of stomach pain, and one case of lack of efficacy. No other information or actual case reports were provided. It is unclear why "lack of efficacy" is a serious case. A review of the line listings of AEs revealed the following:

- mentions of hair loss/alopecia, frequent mentions of rash, but no specific case of TENS
- mentions of decreased/blurry vision; some with resolution, others of unknown outcomes
- numerous GI complaints, a few mentions of hematemesis, melaena, blood in stool, tongue black/brown/swollen, and one mention of an increase in amylase
- mentionsof increased bilirubin/jaundice, hepatitis with no outcome described, and one mention of biliary pain which resolved
- one mention of neonatal thrombocytopenia which resolved. Mother took omeprazole throughout pregnancy
- one mention of gastric polyp with no other information

CONCLUSIONS/DISCUSSION

Omeprazole is generally considered a safe and very effective drug and had been approved recently for long term maintenance therapy. There has been extensive experience with the use of omeprazole capsules worldwide in the last 12 years (300 million treatments). Omeprazole-magnesium MUPS tablets have not been approved for the U.S. market, but is available outside of the U.S. (12 million treatments in the last 2 years). There is also post-marketing experience with omeprazole-magnesium in a delayed release formulation, which is different from the MUPS formulation, in Canada; 6.4 million treatments up to 1/98. As noted in sponsor's submission, the most frequently reported AEs from post-marketing experience has been diarrhea, headache, nausea, abdominal pain, and rash, all of which are listed in current Rx labeling.

The post-marketing experience of the MUPS tablet formulation overall confirms this adverse event pattern. There were cases of serious adverse events in people who switched from the use of omeprazole capsules to the MUPS tablet formulation. Most of these SAEs resolved upon discontinuation of the specific formulation. The full extent of the occurrence of all AEs with a change in formulation to MUPS cannot be assessed since adequate information to do so was not provided by the sponsor.

Much of the adverse events described were known and listed in prescription labeling. However, the post-marketing experience does reflect that rare but very serious, and even fatal cases do occur, in association with the use of omeprazole-magnesium MUPS tablets, albeit in the setting of multiple medical conditions and multiple concomitant medications. While these very serious events involving the liver, pancreas, bone marrow, and skin were considered rare events, the potential for much larger numbers of exposures and thus many more of these events could result from much expanded use by a general population once this drug is available OTC.

Availability in the OTC market invariably results in much greater product sales and therefore much greater exposures by the lay public, without benefit of a learned intermediary to assess their particular risk/benefit situation. One should be assured that, despite easier availability and greater exposures, the overall benefit far outweigh the risks. The sponsor should provide some consideration or estimation of serious events that may be expected with widespread OTC availability to the general public.

RECOMMENDATIONS

The sponsor should provide a reporting rate of the total AEs, SAEs, and deaths relative to the number of treatments prescribed for the MUPS formulation. Based on the experience of similar drug products that have undergone Rx-to-OTC marketing, and the expectation of increased sales with OTC availability, some measure of expected risk/serious events should be estimated. Phase IV surveillance actively monitoring for these serious and potentially fatal cases may need to be in place, so that corrective measures can be instituted in a timely fashion.

Appendix 1

(Registration Life Cycle) Name Contains 'omeprazole'
(Registration Life Cycle) Retracted Date Is No Date '*'
Where the Registration Life Cycles have Registration Submission Records with:
(Registration Submission Record) Purpose Is 'Application'
and the Registration Submission Records have the following product(s):
omeprazole gastro-resistant capsule hard 10 mg, omeprazole gastro-resistant capsule hard 20 mg, omeprazole gastro-resistant capsule hard 40 mg

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Algeria	omeprazole gastro-resistant capsule hard 20 mg		1993-01-01	1994-02-01
Argentina	omeprazole gastro-resistant capsule hard 10 mg	1995-07-21	1996-01-22	1996-04-01
Argentina	omeprazole gastro-resistant capsule hard 20 mg		1989-12-28	1990-03-30
	omeprazole gastro-resistant capsule hard			
Australia	omeprazole gastro-resistant capsule hard 10 mg	1993-04-19	1994-07-04	1996-02-01
Australia	omeprazole gastro-resistant capsule hard 20 mg	1987-08-31	1988-12-01	1990-05-30
Australia	omeprazole gastro-resistant capsule hard 40 mg	1996-11-29	1997-08-27	1999-03-01
Austria	omeprazole gastro-resistant capsule hard 10 mg	1993-06-29	1995-05-23	1995-10-01
Austria	omeprazole gastro-resistant capsule hard 20 mg	1986-12-12	1990-12-17	1991-06-01
Austria	omeprazole gastro-resistant capsule hard 40 mg	1991-05-22	1993-12-06	1995-10-01
Bahamas	omeprazole gastro-resistant capsule hard 20 mg		1992-03-01	1992-10-01
	omeprazole gastro-resistant capsule hard			
Bahrain	omeprazole gastro-resistant capsule hard 20 mg	1990-01-01	1992-01-07	1993-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Barbados	omeprazole gastro-resistant capsule hard 20 mg		1992-03-01	1992-10-01
Belgium	omeprazole gastro-resistant capsule hard 10 mg	1994-11-24	1996-12-11	1997-06-01
Belgium	omeprazole gastro-resistant capsule hard 20 mg	1986-11-01	1988-12-01	1989-10-30
Belgium	omeprazole gastro-resistant capsule hard 40 mg	1993-05-06	1995-02-21	1997-02-15
	omeprazole gastro-resistant capsule hard			
Brazil	omeprazole gastro-resistant capsule hard 10 mg	1993-05-26	1993-08-26	1994-08-01
Brazil	omeprazole gastro-resistant capsule hard 20 mg	1988-03-14	1990-02-21	1990-10-11
Brazil	omeprazole gastro-resistant capsule hard 40 mg	1994-07-14	1996-10-17	1997-03-06
Cameroon	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-02-01
	omeprazole gastro-resistant capsule hard			
Canada	omeprazole gastro-resistant capsule hard 20 mg	1987-03-01	1989-06-13	1989-06-30
	omeprazole gastro-resistant capsule hard			

Country	Drug	Submission date	Date of approval/launch	Launch date
Chile	omeprazole gastro-resistant capsule hard		1990-07-26	1990-11-01
	omeprazole gastro-resistant capsule hard 20 mg			
China	omeprazole gastro-resistant capsule hard		1988-07-27	1990-01-01
Colombia	omeprazole gastro-resistant capsule hard 20 mg	1990-01-01	1996-11-07	1998-01-01
Colombia	omeprazole gastro-resistant capsule hard 10 mg		1991-07-08	1993-08-01
	omeprazole gastro-resistant capsule hard 20 mg			
Congo	omeprazole gastro-resistant capsule hard		1989-01-01	1989-02-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Cyprus	omeprazole gastro-resistant capsule hard 20 mg		1989-05-18	1989-09-01
	omeprazole gastro-resistant capsule hard			
Czech Republic	omeprazole gastro-resistant capsule hard 10 mg	1995-02-15	1996-02-14	1996-09-01
Czech Republic	omeprazole gastro-resistant capsule hard 20 mg	1990-06-17	1992-06-17	1993-03-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Ecuador	omeprazole gastro-resistant capsule hard 20 mg	1994-09-22	1994-12-09	1995-06-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Egypt	omeprazole gastro-resistant capsule hard 20 mg	1988-06-01	1991-02-26	1992-01-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard		1992-07-28	1992-11-01
El Salvador	omeprazole gastro-resistant capsule hard 20 mg			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
France	omeprazole gastro-resistant capsule hard 10 mg	1993-07-22	1996-03-13	1997-10-01
France	omeprazole gastro-resistant capsule hard 20 mg	1986-12-12	1987-04-15	1989-12-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard 20 mg			
Gabon	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-02-01

Country	Name			
Germany	omeprazole gastro-resistant capsule hard 10 mg	1993-04-12	1997-03-05	1997-04-15
Germany	omeprazole gastro-resistant capsule hard 20 mg	1986-08-14	1989-10-06	1989-11-01
Germany	omeprazole gastro-resistant capsule hard 40 mg	1990-10-01	1993-02-22	1993-04-01
	omeprazole gastro-resistant capsule hard			
Greece	omeprazole gastro-resistant capsule hard 20 mg	1988-11-22	1989-10-30	1990-04-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Guatemala	omeprazole gastro-resistant capsule hard 20 mg		1991-09-30	1992-02-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Hong Kong	omeprazole gastro-resistant capsule hard 10 mg		1996-01-22	1996-01-22
Hong Kong	omeprazole gastro-resistant capsule hard 20 mg	1987-09-30	1989-01-20	1989-03-01
	omeprazole gastro-resistant capsule hard			
Hungary	omeprazole gastro-resistant capsule hard 20 mg	1989-12-04	1991-07-05	1991-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Indonesia	omeprazole gastro-resistant capsule hard 20 mg	1987-09-30	1988-12-24	1990-10-01
Iran	omeprazole gastro-resistant capsule hard 20 mg			1993-06-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Ireland	omeprazole gastro-resistant capsule hard 10 mg	1993-07-27	1994-07-25	1994-10-04
Ireland	omeprazole gastro-resistant capsule hard 20 mg	1987-06-01	1989-03-16	1989-06-01
Ireland	omeprazole gastro-resistant capsule hard 40 mg	1990-10-11	1992-02-21	1994-04-20
	omeprazole gastro-resistant capsule hard 10 mg			
Israel	omeprazole gastro-resistant capsule hard 20 mg		1990-07-01	1992-04-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Italy	omeprazole gastro-resistant capsule hard 20 mg	1991-03-27	1993-04-17	1993-05-01
	omeprazole gastro-resistant capsule hard			
Ivory Coast	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1989-09-01
	omeprazole gastro-resistant capsule hard			
Jamaica	omeprazole gastro-resistant capsule hard 20 mg	1991-05-01	1991-07-05	1992-03-01
	omeprazole gastro-resistant capsule hard			

	omeprazole gastro-resistant capsule hard			
Jordan	omeprazole gastro-resistant capsule hard 20 mg	1992-11-01	1993-12-01	1994-05-01
	omeprazole gastro-resistant capsule hard			
Kenya	omeprazole gastro-resistant capsule hard 10 mg	1996-07-01	1997-02-20	1997-06-01
Kenya	omeprazole gastro-resistant capsule hard 20 mg	1988-12-01	1992-07-29	1992-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Kuwait	omeprazole gastro-resistant capsule hard 20 mg	1993-03-01	1993-06-01	1993-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Lebanon	omeprazole gastro-resistant capsule hard 20 mg	1988-11-01	1991-02-01	1991-06-01
Libya	omeprazole gastro-resistant capsule hard 20 mg		1993-05-08	1995-01-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Luxembourg	omeprazole gastro-resistant capsule hard 10 mg	1993-04-27	1995-07-19	1997-11-01
Luxembourg	omeprazole gastro-resistant capsule hard 20 mg	1987-02-01	1987-11-16	1988-02-01
Luxembourg	omeprazole gastro-resistant capsule hard 40 mg		1993-01-07	1993-07-01
	omeprazole gastro-resistant capsule hard			
Malaysia	omeprazole gastro-resistant capsule hard 20 mg	1988-05-11	1989-05-27	1990-05-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Mexico	omeprazole gastro-resistant capsule hard 20 mg	1987-01-01	1990-07-01	1991-01-01
	omeprazole gastro-resistant capsule hard			
Morocco	omeprazole gastro-resistant capsule hard 20 mg		1992-01-01	1993-02-01
Netherlands	omeprazole gastro-resistant capsule hard 10 mg	1993-04-01	1994-02-15	1994-02-28
Netherlands	omeprazole gastro-resistant capsule hard 20 mg	1986-10-01	1988-11-10	1988-12-01
Netherlands	omeprazole gastro-resistant capsule hard 40 mg	1990-06-26	1991-06-18	1992-04-01
Netherlands Antilles	omeprazole gastro-resistant capsule hard 20 mg		1991-06-13	1991-08-15

Netherlands Antilles	omeprazole gastro-resistant capsule hard 40 mg		1993-01-27	1993-02-01
	omeprazole gastro-resistant capsule hard			
New Zealand	omeprazole gastro-resistant capsule hard 10 mg	1996-07-05	1997-01-13	1998-01-01
New Zealand	omeprazole gastro-resistant capsule hard 20 mg	1986-11-05	1990-04-19	1990-12-01
New Zealand	omeprazole gastro-resistant capsule hard 40 mg	1997-04-27	1997-10-21	1998-01-01
	omeprazole gastro-resistant capsule hard			
Nigeria	omeprazole gastro-resistant capsule hard 20 mg	1994-03-16	1994-07-29	1994-11-01
	omeprazole gastro-resistant capsule hard 10 mg			
Oman	omeprazole gastro-resistant capsule hard 20 mg	1992-09-27	1993-09-16	1993-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Pakistan	omeprazole gastro-resistant capsule hard 20 mg	1988-11-23	1990-04-17	1991-08-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Panama	omeprazole gastro-resistant capsule hard 20 mg		1992-05-18	1994-06-14
Paraguay	omeprazole gastro-resistant capsule hard 20 mg		1989-12-01	1990-09-01
Peru	omeprazole gastro-resistant capsule hard 10 mg	1996-01-04	1996-01-11	1996-10-01
Peru	omeprazole gastro-resistant capsule hard 20 mg	1994-05-12	1994-06-14	1994-11-01
	omeprazole gastro-resistant capsule hard			
Philippines	omeprazole gastro-resistant capsule hard 10 mg	1993-04-13	1993-10-26	1995-08-01
Philippines	omeprazole gastro-resistant capsule hard 20 mg	1987-11-01	1988-11-02	1989-03-01
Poland	omeprazole gastro-resistant capsule hard 10 mg	1995-10-09	1997-10-28	1998-02-01
Poland	omeprazole gastro-resistant capsule hard 20 mg	1988-11-01	1991-03-12	1991-04-01
	omeprazole gastro-resistant capsule hard			
Portugal	omeprazole gastro-resistant capsule hard 20 mg	1987-10-28	1988-10-04	1989-01-12
Portugal	omeprazole gastro-resistant capsule hard 40 mg	1994-07-27	1998-11-03	1999-11-01
	omeprazole gastro-resistant capsule hard			
Qatar	omeprazole gastro-resistant capsule hard 20 mg	1989-02-11	1991-06-01	1992-05-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			

	omeprazole gastro-resistant capsule hard			
Russia	omeprazole gastro-resistant capsule hard 20 mg	1998-09-22	1993-08-11	1993-08-11
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Saudi Arabia	omeprazole gastro-resistant capsule hard 20 mg	1998-01-14	1991-06-17	1991-10-06
	omeprazole gastro-resistant capsule hard			
Senegal	omeprazole gastro-resistant capsule hard 20 mg		1989-01-01	1990-03-01
Singapore	omeprazole gastro-resistant capsule hard 10 mg		1996-09-11	1997-10-01
Singapore	omeprazole gastro-resistant capsule hard 20 mg	1988-04-22	1988-05-25	1989-03-01
	omeprazole gastro-resistant capsule hard			
Slovakia	omeprazole gastro-resistant capsule hard 20 mg		1992-06-17	1993-03-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
South Korea	omeprazole gastro-resistant capsule hard 20 mg	1987-09-30	1989-02-15	1989-05-06
	omeprazole gastro-resistant capsule hard			
Spain	omeprazole gastro-resistant capsule hard 20 mg	1987-03-04	1989-10-17	1989-11-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Sri Lanka	omeprazole gastro-resistant capsule hard 20 mg		1991-10-01	1992-01-01
	omeprazole gastro-resistant capsule hard			
Taiwan	omeprazole gastro-resistant capsule hard 20 mg	1987-11-01	1990-03-1[illegible]	1990-06-01
Thailand	omeprazole gastro-resistant capsule hard 10 mg	1996-09-13	1997-12-31	1999-03-23
Thailand	omeprazole gastro-resistant capsule hard 20 mg	1987-11-01	1989-03-03	1989-03-31
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Trinidad	omeprazole gastro-resistant capsule hard 20 mg	1991-05-01	1991-08-28	1992-03-01
Tobago	omeprazole gastro-resistant capsule hard 20 mg	1991-05-01	1991-08-28	1992-01-01
Tunisia	omeprazole gastro-resistant capsule hard 20 mg		1992-01-01	1993-01-01
Turkey	omeprazole gastro-resistant capsule hard 20 mg		1991-01-09	1991-03-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			

UK	omeprazole gastro-resistant capsule hard 10 mg	1993-03-12	1994-01-06	1994-09-01
UK	omeprazole gastro-resistant capsule hard 20 mg	1986-11-01	1989-05-09	1989-06-01
UK	omeprazole gastro-resistant capsule hard 40 mg	1990-09-03	1992-09-10	1993-09-01
	omeprazole gastro-resistant capsule hard			
United Arab Emirates	omeprazole gastro-resistant capsule hard 20 mg	1988-10-01	1991-06-10	1993-10-01
	omeprazole gastro-resistant capsule hard			
Uruguay	omeprazole gastro-resistant capsule hard 20 mg		1990-05-11	1992-11-01
USA	omeprazole gastro-resistant capsule hard 10 mg	1993-08-27	1995-10-05	1995-10-30
USA	omeprazole gastro-resistant capsule hard 20 mg	1987-12-21	1989-09-14	1989-10-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Venezuela	omeprazole gastro-resistant capsule hard 20 mg	1991-09-30	1990-10-01	1990-11-01
	omeprazole gastro-resistant capsule hard			
Vietnam	omeprazole gastro-resistant capsule hard 20 mg	1993-05-29	1995-01-04	1995-01-04
Yemen	omeprazole gastro-resistant capsule hard 20 mg	1992-12-14	1993-11-24	1994-04-01
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
	omeprazole gastro-resistant capsule hard			
Zimbabwe	omeprazole gastro-resistant capsule hard 20 mg		1992-01-20	1993-07-01

Appendix 2

Foreign Marketing Developments – Omeprazole Magnesium Tablets for Prescription Use

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
Argentina	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	31/08/1998	Approved 09/11/1998	30/08/1999
Australia	Losec Tablets	Omeprazole magnesium tablets	10, 20 and 40 mg	08/04/1997	Approved 26/11/1998	01/04/1999
Austria	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	14/02/1997	Approved 24/11/1999	01/01/2000
Belgium		Omeprazole magnesium tablets	10, 20 and 40 mg	06/05/1997	Approved 06/12/1999	
Brazil	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	06/05/1998	Approved 27/11/1998	30/07/1999
	Losec tablets	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
Denmark	Losec	Omeprazole magnesium tablets	10, 20 and 40 mg	03/02/1997	Approved 22/09/1997	09/03/1998

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
		Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
Finland	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	28/04/1997	Approved 15/12/1997	20/05/1998
France	Mopral	Omeprazole magnesium tablets	10 and 20 mg	13/05/1997	Approved 17/12/1997	
Germany	Antra MUPS	Omeprazole magnesium tablets	10 mg 20 mg 40 mg	11/03/1997 16/01/1997 06/02/1997	Approved 16/11/1998	01/12/1998
	Losec MUPS	Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
Hong Kong	Losec MUPS	Omeprazole magnesium tablets	10 and 20 mg	05/10/1998	Approved 19/02/1999	30/04/1999 (10,20 mg)
	Losec MUPS	Omeprazole magnesium tablets				
Iceland	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	30/10/1997	Approved 07/10/1998	30/10/1998
	Losec MUPS	Omeprazole magnesium tablets				
Ireland	Losec	Omeprazole magnesium tablets	10, 20 and 40 mg	28/11/1997	Approved 17/09/1999	30/09/1999

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
		Omeprazole magnesium tablets				
Kuwait	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	30/05/1998	Approved 31/05/1999	
		Omeprazole magnesium tablets				
Lithuania	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	05/03/1998	Approved 22/10/1998	
Malaysia	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	09/04/1999	Approved 27/08/1999	01/09/2000
Mexico	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	05/12/1997	Approved 12/06/1998	01/06/1999
	sec MUPS	Omeprazole magnesium tablets				
Netherlands	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	01/05/1997	Approved 26/05/1998	30/05/1999
		Omeprazole magnesium tablets				
Norway	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	24/01/1997	Approved 04/03/1998	01/09/1998
		Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
		Omeprazole magnesium tablets				
	Losec MUPS	Omeprazole magnesium tablets				
Russia	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	24/09/1998	Approved 19/03/1999	28/02/2000
Singapore	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	28/05/1998	Approved 27/01/1999	
		Omeprazole magnesium tablets				
		Omeprazole magnesium tablets				
South Africa	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	01/04/1997	Approved 11/03/1999	01/04/1999
	Losec MUPS	Omeprazole magnesium tablets				
Sweden	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	30/04/1997	Approved 19/12/1997	02/02/1998 (20 mg) 01/05/1998 (10/40 mg)
Switzerland	Antra MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	07/03/1997	Approved 19/12/1997	01/01/1999
		Omeprazole magnesium tablets				
Thailand	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	02/06/1998	Approved 06/09/1999	
	Losec	Omeprazole magnesium tablets				

Country	Trade Name	Formulation	Dosage/Strength(s)	Submission Date (dd/mm/yyyy)	Status/Date	Date Launched (dd/mm/yyyy)
UK	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	17/10/1997	Approved 07/10/1998	30/08/1999
Venezuela	Losec MUPS	Omeprazole magnesium tablets	10, 20 and 40 mg	12/08/1998	Approved 10/05/1999	

M. Walsh

Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Review

JUN 14 2000

Date of submission: April 14, 2000

NDA: 21-229

Sponsor: Proctor and Gamble

Drug: Omeperazole magnesium tablets (Prilosec 1 ™)

Pharmacologic category: Anti- secretory

Proposed indications: For the prevention and relief of heartburn

Materials reviewed: Submission dated April 14, 2000 Waiver for request for pediatric testing of Prilosec 1.

Reviewer: Lawrence Goldkind, M.D.

The sponsor has requested a waiver for pediatric study under age 12. The sponsor claims that:

1. Pediatric populations above the age of 12 are represented in the clinical trials and actual use studies. This population in included in the proposed label.
2. Heartburn in pediatric populations under the age of 12 severe enough to require medication should be evaluated by a physician and treatment overseen by a health care professional.
3. Other treatments such as antacids and H2RA (Pepcid) are approved for the treatment of heartburn in pediatric patients.
4. Prilosec 1 is not likely to be used in a substantial number of pediatric patients with episodic heartburn. The sponsor quoted IMS data for the calendar year 1999 stating that [redacted] of heartburn occurred in the 0-11year old population.
5. Rx omeprazole is under study in the pediatric population for the GERD indication. Studies have shown that omeprazole capsules and magnesium tablets have similar bioavailability.

Reviewer Comments:

Informal consultation with Linda Katz, deputy director of the Division of Over- The-Counter (OTC) Drugs revealed that other acid suppressing drugs, different than antacids, have been excluded form OTC labeling for several interrelated reasons:

1. heartburn has a different differential diagnosis in children under the age of 12 than in adults and therefore requires medical evaluation before therapy
2. the elicitation of heartburn symptoms in pediatric populations under the age of 12 is inadequate for OTC requirements
3. risks to pediatric populations of systemic therapy may be different than to adults

Therefore, the request for waiver for pediatric study of Prilosec 1 is reasonable and consistent with policies of the OTC division regarding previous acid lowering/heartburn products.
However, Prilosec 1 is the first proton pump inhibitor to be evaluated for OTC use. New issues that may relate to pediatric use may arise during the review of this NDA. Furthermore, a more formal discussion with the OTC division is warranted before considering the final requirements for pediatric study under the age of 12 years. The OTC division is considering changes to the current approach to OTC labeling for heartburn treatments. It would be prudent to defer rather than waive pediatric studies until division level meetings between HFD-180 and HFD-560 later in the review of the current NDA submission.

Recommendation for regulatory action:
The sponsor should be informed that the decision regarding the need for pediatric studies is deferred until completion of the review of the current NDA.

[/S/] 6/13/00
Lawrence Goldkind M.D.

cc:
NDA 21-229
HFD-180
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/LGoldkind
HFD-181/MWalsh
HFD-180/JChoudary
HFD-180/LZhou
f/t 6/13/00 jgw
N/21229006.0LG

Concur. June 13, 2000

f/t 6-14-00

[/S/]

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

Table of Contents:

Study #067

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

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

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

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

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

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

Inclusion Criteria

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

Exclusion Criteria

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

Comments

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

Visit 1 (Screening Visit)

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

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

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

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

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

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

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

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

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

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

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

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

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

Results
The following chart displays disposition of the subjects.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4. Summary of Extent of Exposure

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

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

Table 5. Summary of Adverse Events

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

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

Table 6. Adverse Events by Body System

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

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

Table 7. Adverse Events by Body System and COSTART Term

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

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

Deaths
There were no deaths reported.

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

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

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

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

Drug-Demographic Interactions/Drug-Drug Interactions

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

Summary of Study #067

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

Study #014

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

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

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

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

Design

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

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

Visit 1

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

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

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

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

Exclusion Criteria
Subjects were excluded from the study if they:

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Results

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

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

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

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

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

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

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

Table 1. Reasons for Discontinuation

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

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

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

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

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

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

Table 2. Demographics Characteristics (ITT Population)

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

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

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

Table 3. Concurrent Use of Other Heartburn Medications

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

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

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

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

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

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

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

Consistency with Label Use Directions
The term 'consistency' is used in this report to describe the subjects' adherence to the label use directions. Subjects were considered consistent with the three labeled

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

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

Table 4. Consistency with Label Use Directions

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

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

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

Table 5. Consistency with Label Use Directions by Demographics

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 8. Summary of Extent of Exposure

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

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

Table 9. Summary of Adverse Events

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

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

Table 10. Adverse Events by Body System

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

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

Table 11. Adverse Events by Body System and COSTART Term

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

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

Deaths
There were no deaths reported.

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

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

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

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

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

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

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

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

Summary of Study #014

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

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

Study #022

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Children under 12 years of age: Ask a doctor.

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

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

Interim Phone Interview

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

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

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

Visit 2

Subjects had the following procedures performed during this visit:

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

Statistical Methods and Analysis Plans

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

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

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

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

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

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

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

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

Determination of Sample Size

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

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

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

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

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

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

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

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

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

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

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

Results

The following diagram displays a disposition of the subjects.

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

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

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

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

Table 1. Reasons for Discontinuation

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

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

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

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

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

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

Demographic Characteristics

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

Table 2. Demographic Characteristics (ITT Population)

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

Heartburn History

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

Prior and Concomitant Therapies

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 4. Consistency with Label Use Directions by Demographics

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Efficacy Evaluation

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

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

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

Concurrent Use of Heartburn Medication

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

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

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

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

Table 7. Summary of Extent of Exposure

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

Table 8. Summary of Adverse Events

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

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

Table 9. Adverse Events by Body System

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

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

Table 10. Adverse Events by Body System and COSTART Term

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

Deaths

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

Other Serious Adverse Events

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

Subject Number **002104**

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

Subject Number **002147**

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

Discontinuation Due To Adverse Events

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

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

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

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

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

Comments

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

Summary of Study #022

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

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

Study 091

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

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

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

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

Visit 1
The following procedures were performed during Visit 1:

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

Inclusion Criteria

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

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

Exclusion Criteria

Subjects were excluded from the study if they:

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

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

Visit 2

Subjects had the following procedures performed during Visit 2.

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

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

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

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

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

Prior and Concomitant Therapy

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

Usage Patterns and Acceptance and Liking Attributes

Usage patterns were collected and summarized to determine:

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

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

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

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

Safety was investigated by evaluating all reported AEs. Verbatim terms on the CRFs were linked to preferred terms and related body systems using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) mapping system. All reported AEs were summarized by the number of subjects reporting AEs, intensity, relationship to study medication, and body system for each usage group. All subjects taking study medication were included in the safety analysis.

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

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

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

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

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

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

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

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

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

Table 1. Reasons for Discontinuation of the study

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

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

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

Table 2. Demographic Characteristics (ITT Population)

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

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

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

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

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

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

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

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

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

3) dosed for no more than 14 consecutive days.

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

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

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

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

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

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

Product Use Summary

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

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

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

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

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

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

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

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

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

Table 6. Summary of Adverse Events

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

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

Deaths
There were no deaths.

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

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

Summary of Study #091

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

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

[/S/]
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ON ORIGINAL

180/ M. WALSH

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OPDRA POSTMARKETING SAFETY REVIEW**	
TO: Lilia Talarico, M.D., Director Division of Gastrointestinal and Coagulation Drug Products HFD-180	**FROM:** Ann Corken, RPh, MPH, Safety Evaluator Mary Willy, PhD, Epidemiologist Ron Wassel, Pharm.D, Safety Evaluator Division of Drug Risk Evaluation I I (DDREII) HFD-440	OPDRA PID # D000223

DATE REQUESTED:
March 15, 2000

AUG 14 2000

NDA #19-810 **SPONSOR: MERCK**

DRUG :
OMEPRAZOLE (PRILOSEC)

EVENT:
EVALUATION OF SAFETY PROFILE FOR OTC SWITCH CONSIDERATION

Executive Summary: This consult was prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review selected adverse events for omeprazole as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole up to March 31, 2000; 10,005 reports were identified in the database. Both domestic and foreign experience is addressed in this document, however, the focus is on the domestic experience.

The following issues have been reviewed in this consult: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For many of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole; many patients had underlying conditions or were taking concomitant medications which could have contributed to the events. Summary of these issues appears at the end of each section. The most compelling issue reviewed was serious liver events, which were temporally related to omeprazole use and included serious outcomes such as liver transplants, deaths, and encephalopathy. Serious liver events are included in the current labeling for omeprazole. The pediatric cases reviewed tended to mirror events seen in adults; these typically were not healthy children prior to omeprazole use.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that there was a trend for larger numbers of reports with a longer duration of omeprazole use, however, conclusions cannot be made because the data was derived from small numbers of spontaneous reports in the system. A review of the literature for omeprazole-related cancer revealed that the studies had limited numbers of patients exposed for short time periods with limited follow-ups. A review of the studies and case reports in the literature for delays in GI cancer diagnosis due to patient self-medication revealed that both prescription and OTC use of antacid drugs may delay diagnosis; additional studies are needed. Data regarding congenital anomalies will be addressed in a separate document.

Given the number of years that omeprazole has been on the market (11 years) and its extensive use (——— prescriptions), AERS report data suggest that the frequency of serious adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, underreporting must be considered.

Reason for Request/Review:
Omeprazole (Prilosec) is indicated to treat duodenal ulcer and gastric ulcer, symptomatic GERD, erosive esophagitis, pathological hypersecretory conditions, and for maintanence of healing of erosive esophagitis. It is marketed by Astra Merck and was approved on September 14, 1989. Division HFD-180 has requested a review of selected adverse events for omeprazole because Astra Merck has petitioned for an Rx to OTC switch.

Reviewers' Signatures / Date:	Team Leader's Signature / Date:
/S/ 8/11/2000 Ann Corken, RPh, M.P.H. Mary Willy, Ph.D. /S/ Ron Wassel, Pharm.D.	/S/ 8/11/2000 Toni Piazza-Hepp, Pharm.D.

Division Director Signature / Date: /S/ 8/14/2000

Evelyn Rodriguez, M.D., M.P.H.

Cc: NDA # 19-810
HFD-180 Division File/Div Dir / MO / SMO / Project Manager
HFD-560 Division File/Div Dir / MO / SMO / Project Manager
HFD-440 Rodriguez/Willy/Corken/Wassel/Piazza-Hepp/Chron/Drug
HFD-400 Honig

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TABLE OF CONTENTS

1.0 LABELING

The current Prilosec labeling contains the following events in the ADVERSE REACTIONS section relating to the corresponding body systems discussed in this review:

Hematologic—Rare instances of pancytopenia, agranulocytosis (some fatal)

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

Gastrointestinal—Pancreatitis (some fatal)

Skin—Rarely, cases of severe generalized skin reactions including toxic epidermal necrolysis (TEN; some fatal), Stevens-Johnson syndrome, and erythema multiforme (some severe)

Special senses—Tinnitus

Under PRECAUTIONS:

Drug Interactions—Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been clinical reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporine, disulfiram, benzodiazepines). Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Pediatrics - Safety and effectiveness in pediatric patients have not been established.

Pregnancy Category C - Teratology studies conducted in pregnant rats at doses up to 138 mg/kg/day (approximately 345 times the human dose) and in pregnant rabbits at doses up to 69 mg/kg/day (approximately 172 times the human dose) did not disclose any evidence for a teratogenic potential of omeprazole. In rabbits, omeprazole in a dose range of 6.9 to 69.1 mg/kg/day (approximately 17 to 172 times the human dose) produced dose-related increases in embryo-lethality, fetal resorptions and pregnancy disruptions. In rats, dose-related embryo/fetal toxicity and postnatal developmental toxicity were observed in offspring resulting from parents treated with omeprazole 13.8 to 138.0 mg/kg/day (approximately 35 to 345 times the human dose). There are no adequate or well-controlled studies in pregnant women. Sporadic reports have been received of congenital abnormalities occurring in infants born to women who have received omeprazole during pregnancy. Omeprazole should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Carcinogenesis - The labeling refers to studies in rats, at daily doses approximately 4 to 352 times the human dose, which produced gastric ECL cell carcinoids in a dose-related manner (incidence higher in female rats, which had higher blood levels of omeprazole). Gastric carcinoids seldom occurred in the untreated rat.

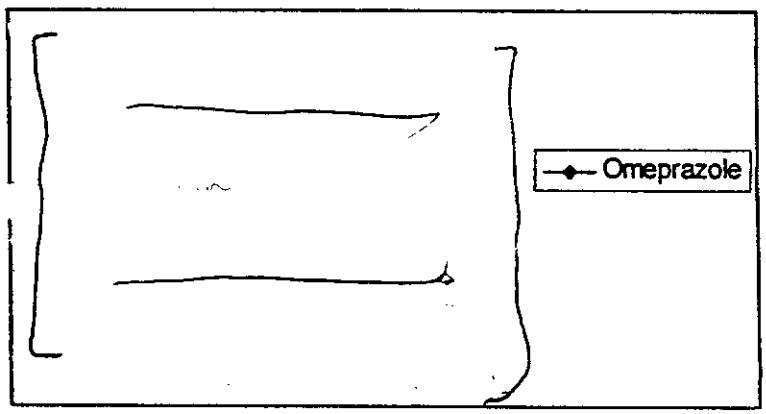
2.0 INTERNATIONAL EXPERIENCE

To date, Sweden is the only country that has granted nonprescription status to omeprazole. The MUPS dosage form (10 and 20 mg) of omeprazole was approved in April 2000 for the prevention and treatment of heartburn. Since the switch was recent, there are no data regarding nonprescription use in Sweden.

3.0 DRUG USE

The chart below summarizes projected total prescriptions of omeprazole dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S. from January 1, 1990 through March 31, 2000. A total of [redacted] prescriptions have been filled in the specified time period.

*Jan-Mar



The table below represents projected estimated proportion of omeprazole use by gender from January 1, 1989 through March 31, 2000.

Total % Use by Gender	
Female	[redacted]
Male	[redacted]
Unspec	[redacted]
Total	[redacted]

The table below shows projected estimated proportion of omeprazole use by age category from January 1, 1989 through March 31, 2000.

Total% Use by Age Bracket (in years)	
00 to 10	<1%
11 to 20	
21 to 30	
31 to 40	
41 to 50	
51 to 60	
61 to 70	
71 to 80	
81 to 90	
91 to 100	
101-110	
Unspec	
Total	

This information is from IMS Health National Prescription Audit Plus (on-line) and National Disease and Therapeutic Index and is not to be used outside of the FDA without prior clearance by IMS Health.

4.0 ADVERSE EVENTS OVERVIEW

There are a total of 10,005 adverse reaction reports of any nature for omeprazole from time of marketing through March 31, 2000 in the Adverse Event Reporting System (AERS). A total of 579 reports with a death outcome will be further discussed in this document. More than half (5431) of the reports were received from the U.S.; 533 of the reports were received from France, 298 of the reports were received from the United Kingdom, 203 of the reports were received from Germany, and 180 of the reports were received from Japan. Attachment A is a listing of MEDDRA Preferred terms (PT) by decreasing order of frequency where there were 10 or more cases per event in AERS. Since these are raw figures from AERS, some of the numbers may represent duplicates.

5.0 DEATH OUTCOME CASES

AERS was searched for reports involving omeprazole that were received by the FDA up through and including March 31, 2000 and resulted in an outcome of death. A total of 579 reports were retrieved. From these results, a search was conducted to separate the data into domestic and foreign reports, which resulted in the identification of 184 domestic reports. The remaining 395 foreign reports is a raw number and does not reflect the actual number of cases (no attempt was made to review these reports). Reviewing these 184 domestic reports identified 98 unduplicated cases. Of the 98 cases, 52 were excluded from further review for the following reasons: 3 cases that were actually foreign reports, 3 cases that were incorrectly entered into AERS as having a death outcome, 1 case in which the adverse event that led to the patient's death (bone marrow depression) was present prior to omeprazole therapy, and the remainder in which the patient's death was not related to the use of omeprazole but rather their underlying disease such as sepsis or carcinoma. The remaining 46 cases were analyzed for cause of death and are discussed below.

5.1 Gastric carcinoma (n = 3)

Three cases, although probably not omeprazole–related deaths, are of interest to report here in that they involved the use of omeprazole for stomach pain in which the patients eventually died due to gastric carcinoma. Two of these cases (one unknown demographics; one 46-year-old male) involved short–term omeprazole use with no relief of pain and were eventually diagnosed with the malignancy. One case (unknown demographics) was described as the "patient died from stomach cancer after two and a half years of therapy with omeprazole."

Another case involved an 80-year-old male who took omeprazole 20 mg daily for seven years for the treatment of gastroesophageal reflux disease. The patient was eventually diagnosed with "abdominal carcinomatosis" with a biopsy revealing "adeno-carcinoid carcinoma." The patient had a history of pancreatic cancer treated with four courses of chemotherapy and had documented "carcinomatosis of the peritoneal cavity." Two years after the original diagnosis of abdominal carcinomatosis, biopsies of the gastric body and antrum revealed "mild to moderate chronic gastritis with no malignancies, no metastatic disease, no intestinal metaplasia, no helicobacter and no mention of enterochromaffin cell hyperplasia or carcinoid." The reporter indicated the patient died from "probable poorly differentiated neuroendocrine carcinoma of unknown primary."

5.2 Complications of pregnancy (n = 4)

There were four cases involving the death of a fetus or infant in which the women took omeprazole during their pregnancy. Two of the cases were stillbirths, one case involved a child born with hydranencephaly who died on day 1, and one case of a child born with a hypoplastic heart who eventually died on day 74 following numerous open heart procedures.

5.3 Drug interactions (n = 9)

There were nine cases in which the death outcome may have been due to a drug interaction. Each of the offending drugs is involved in the cytochrome P-450 metabolic pathway. Six of the cases reported the cause of death as cardiac arrest or sudden death. In these six cases, four involved cisapride, one involved amitriptyline, and one involved nicardipine. The other three cases in which the cause of death was not reported involved one case each of the use of omeprazole with fluconazole, clarithromycin, and cisapride.

5.4 Hepatic failure (n = 8)

Demographic data

AGE (years) (n = 7):	Range—48 to 83 years; Median—66 years; Mean—66
SEX:	Female—4; Male—4
REPORTING YEAR:	1990—2; 1992, 1996, 1997—1 each; Unknown—3
REACTION ONSET (DAYS) (n=5):	Range—7 to 150 (approx.) days; Median—13 days; Mean—48 days (approx.)
DOSE PER DAY (n = 7):	20 mg—6; 40 mg—1

In six of the eight cases there were possible confounding factors including a history of alcohol abuse (two cases), a history of liver disease (two cases), and concomitant drug therapy that has been associated with liver dysfunction (one case with pravastatin and one case with quinapril).

Representative Case of Hepatic Failure Death

Case# 5336663 (Mfr.# 19951100203) A 62-year-old male with a history of intermittent epigastric and right upper quadrant pain associated with reflux symptoms unsuccessfully treated with ranitidine, erosive esophagitis, hypertension, and coronary artery disease was placed on therapy with omeprazole 20 mg daily. Other medication, which the patient had been taking for over one year, included atenolol, diltiazem, and aspirin. Seventeen days after starting omeprazole, the patient was hospitalized with a four day history of worsening epigastric pain, anorexia, nausea and vomiting, and one day of weakness and dizziness. The patient denied any history of hepatitis, blood transfusions, toxin exposures, alcohol or acetaminophen use. He was alert with a mild slowing of mentation and a slight flapping tremor. By the next morning he was obtunded. His ammonia had reached 238 micromol/L and his asterixis was much more marked. He was transferred to another hospital for a possible liver transplant, but no liver donor was available. Hepatitis serologies were all negative. His hospital course was complicated by respiratory failure, oliguric renal failure, and seizures and he died five days after initial presentation. Autopsy revealed severe hepatic necrosis and special stains for other causes were negative. This was reported in the published article Jochem V, Kirkpatrick R, Greenson J, et al. Fulminant hepatic failure related to omeprazole. Am J Gastroenterology 1992; 87: 523-5.

5.5 Pancytopenia / Bone marrow depression (n = 3)

Demographic data

AGE (years):	Range—60 to 85 years; Median—66 years; Mean—70.3
SEX:	Female—1; Male—2
REPORTING YEAR:	1990—1; 1993—1; Unknown—1
REACTION ONSET (DAYS):	Range—6 to 11 (approx.) days; Median—7 days; Mean—8 days (approx.)
DOSE PER DAY:	20 mg—1; 40 mg—1; 80 mg—1

Two of the cases had potentially confounding drug therapy with known adverse hematologic effects including the use of nortriptyline and ranitidine in one case, and multiple drug therapy with several antibiotics in the other.

Representative Case of Bone Marrow Depression Death

Case# 5512622 (Mfr.# 19961100176) An 85-year-old male with upper gastrointestinal bleeding secondary to gastric ulcer disease with gastritis and positive Helicobacter pylori was placed on therapy with omeprazole 20 mg twice a day along with clarithromycin 500 mg three times a day and metronidazole 500 mg three times a day. Six days later the patient was admitted to the hospital because of the following reported lab values: WBC 900 (25% seg), platelets 26,000, bilirubin 7.7, AST 6 times normal, ALT 2.5 times normal, and alkaline phosphatase 3 times normal. The patient's bone marrow showed almost complete bone marrow failure and subsequently he died secondary to severe sepsis.

5.6 Congestive heart failure (n = 3)

Demographic data

AGE (years) (n = 2):	54 and 56
SEX:	Female—2; Male—1
REPORTING YEAR:	1990—1; 1994—1; Unknown—1
REACTION ONSET:	6 days; 3 months; 4 years
DOSE PER DAY:	20 mg—1; 40 mg—1; 120 mg—1

In two of the cases the patients had a history of CHF prior to omeprazole therapy, but developed worsening heart failure and eventually died. In the case in which the patient had been taking omeprazole for four years, he had a severe myocardial infarction complicated by several cardiac arrests, which led to poor myocardial function and eventual death from heart failure. Whether omeprazole contributed to diminished cardiac function in any of these cases is unknown.

5.6 Miscellaneous Death Outcome Cases
There was one case of **toxic epidermal necrolysis** in a 77-year-old male after 15 days of omeprazole therapy 20 mg daily.

In another case, a male of unknown age developed an ileus and subsequent **pancreatitis** within one week after initiation of omeprazole therapy. Concomitant therapy included Augmentin, furosemide and an unspecified steroid for what was believed to be an immune-related thrombocytopenia. He was hospitalized, underwent surgery and died post-operatively.

There were two cases of deaths following **gastrointestinal hemorrhage** in patients of unknown age and gender. In one case omeprazole was given after intravenous cimetidine was used to treat the hemorrhage, but the patient subsequently experienced another hemorrhage and died. In the other case it is unclear whether the patient bled while on omeprazole or was being treated for the bleeding with omeprazole and eventually died.

An 87-year-old male treated with omeprazole 20 mg daily for approximately 8 months died from a **"gastric outlet obstruction and prolonged complications."**

One patient committed **suicide** soon after starting omeprazole.

A case of **lymphoma** occurred in a male patient treated with omeprazole 20 mg daily for approximately 2 years for the treatment of reflux esophagitis.

There were eight poorly documented cases that were generally reported as death occurring while taking omeprazole or shortly after initiating omeprazole therapy. Three of these cases

may have been related to a cardiac arrest or arrhythmia, one case was reported as possibly related to the liver or the kidneys, and one case was noted to have a pain in the leg with subsequent chest pain prior to the patient's death.

5.7 Summary of Death Cases

Of the 46 cases that were reviewed, the most compelling cases had causes of death due to hepatic failure and bone marrow depression. The product labeling for omeprazole includes hepatic failure, pancytopenia/agranulocytosis, toxic epidermal necrolysis and pancreatitis as events with reports of fatalities. Deaths attributed to drug interactions and complications of pregnancy are also noteworthy. The one case of suicide may be of note in that depression is listed in the product labeling. It is difficult to make any kind of determination in the cases of congestive heart failure, gastrointestinal hemorrhage, gastric outlet obstruction, and lymphoma.

In the drug interaction section, mention is made that patients should be monitored to determine the necessity of adjusting the dosage of drugs metabolized by the cytochrome P-450 system when taken concurrently with omeprazole, although few drugs are given as examples (none of which are those that are mentioned above). In regard to pregnancy, the product labeling lists omeprazole as Pregnancy Category C and discusses sporadic reports of congenital abnormalities in humans and embryo/fetal toxicity in animals.

6.0 PEDIATRIC EXPERIENCE

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and age criteria of 0 to 16 years. The search produced 182 reports. These 182 cases were separated into serious (i.e., hospitalization, death, life threatening, disability) and nonserious outcomes; the cases with serious outcomes were separated into domestic and foreign and then checked for duplicates. Among these were 19 cases of congenital anomalies; an assessment of these cases along with other available epidemiologic data on this topic will be provided in a separate document. There were 20 other domestic pediatric cases and 28 foreign cases of a serious nature for review.

6.1 Deaths (n = 8)

There were a total of eight reports of deaths in children receiving omeprazole; seven of these reports were from foreign sources. Three patients died of cardiac arrhythmias; all three patients also were receiving cisapride concomitantly. Two patients died of hematologic events (thrombocytopenia and aplastic anemia); both patients had other serious medical conditions and were taking numerous concomitant medications. Two patients with end-stage renal failure received omeprazole; both patients received other medications that were considered suspect by the reporters. One patient experienced sepsis and died of cardiac arrest. One of the patients described above had received the IV form of omeprazole. These reports also are described below under their respective categories.

6.2 Carcinoma or neoplasms (n = 3)
U.S. experience- There were two cases. A 16-year-old boy developed a gastrin-producing chromafin-cell hyperplasia after taking 40 mg of omeprazole a day for an unknown duration; no other information was available. A 14-year-old boy was thought to have developed gastric carcinoma after taking 20 mg of omeprazole a day for an unknown duration; subsequent tests did not indicate carcinoma.

Foreign experience-One case of a testicular cyst was received through AERS.

6.3 Cardiac events (n = 5)
U.S. experience- A single case was identified of a 7-year-old boy who developed ventricular fibrillation and torsades de pointes and died after receiving 40 mg of omeprazole a day for 2.5 years; he had a history of congenital heart disease and was receiving numerous concomitant medications including cisapride.

Foreign experience-There were two cases of tachycardia, one case of QT prolongation/ asystole/cardiac arrest leading to death; both patients were receiving cisapride. There was one case of cardiac arrest leading to death.

6.4 Gastrointestinal events (n = 6)
U.S. experience-No cases of serious gastrointestinal events were received through AERS.

Foreign experience-There was one case of rectal hemorrhage, one case of severe epigastric pain and nausea, one case of epigastric pain and colic, one case of severe bloating and cramping, one case of hematemesis, and one case of GI hemorrhage reported through AERS; all patients had to be hospitalized because of the event.

6.5 Hematologic events (n = 5)
U.S. experience-There were two cases. A 15-year-old girl experienced thrombocytopenia (platelet count = 80,000) after taking 20 mg of omeprazole a day for two to three weeks; the event abated when omeprazole was discontinued. Her medical history included dyspepsia and Evans Syndrome; concomitant medication included prednisone. A 13-year-old girl experienced anemia, hematuria, lupus-like syndrome, and possible autoimmune syndrome after taking 20 mg of omeprazole a day for approximately three months; her symptoms worsened when omeprazole was replaced with ranitidine. Omeprazole therapy was reinitiated; the patient's outcome was not reported.

Foreign experience-There was one case of thrombocytopenia/leukocytosis, one case of thrombocytopenia, and one case of thrombocytopenia/aplastic anemia received through AERS. Two of these patients died.

Hepatic disorders (n = 2)
U.S. experience-A 15-year-old boy developed hepatitis after taking 20 mg of omeprazole a day for two months; the event abated when omeprazole was discontinued. The report provided very little information regarding the patient's medical history and concomitant medications.

Foreign experience-One case of increased liver enzymes was received through AERS.

6.6 Neurological events (n = 9)

U.S. experience-There were six cases. A 2-year-old boy developed ataxia, gait abnormalities, and coordination problems after taking 7 to 9 mg of omeprazole a day (duration unknown); the events resolved when omeprazole was discontinued and reappeared when omeprazole was reintroduced. Concomitant medications included cisapride, Benadryl, Intal, and Atrovent. The dose was titrated down and the patient continued on therapy without incident. A 12-year-old girl developed breakthrough seizures when omeprazole was added to her medication regimen that included phenytoin; her phenytoin levels were stable, but began fluctuating when omeprazole was introduced. The patient had a history of seizures, encephalopathy, attention-deficit disorder, possible hypothyroidism, and porphyria. She continued on omeprazole; her outcome was not reported. A 3-year-old girl with brain damage developed multiple seizures after taking 20 mg of omeprazole a day (duration not specified); concomitant medication included Depakote. The outcome was not specified; very little information was provided. A 10-year-old boy experienced a change in carbamazepine levels after taking 10 mg of omeprazole a day (duration unknown); his outcome was not reported. He had a history of seizures and was physically disabled; concomitant medications included carbamazepine, terbinafine, and diazepam. A 5-year-old girl experienced seizures (both focal and general) after receiving 20 mg of omeprazole a day (duration unknown); an EEG indicated a diagnosis of benign rolandic epilepsy. Concomitant medication included amoxicillin and Biaxin. Omeprazole was discontinued; the reporter stated that a lowered seizure threshold triggered seizures which is consistent with benign rolandic epilepsy. A 13-year-old girl experienced one seizure among other medical events (consumer report).

Foreign experience-One patient experienced an exacerbation of her movement disorder, one patient experienced extreme vertigo, and another patient experienced an increase in seizure activity.

6.7 Pancreatic events (n = 5)

U.S. experience-There were three cases. An 8-year-old boy with leukemia developed pancreatitis after taking 20 mg of omeprazole a day for six months; concomitant medications and outcome were not reported. A 3-year-old boy developed pancreatitis after taking 20 mg of cisapride a day (duration unknown); his outcome was not reported. His medical history included cerebral palsy, convulsions, and esophageal reflux; concomitant medications included cisapride, valproic acid, and multivitamins. A 14-year-old girl experienced elevated amylase and lipase after taking 40 mg of omeprazole a day for 3 days; she continued to take omeprazole and was diagnosed with pancreatitis 12 days later. The event was beginning to resolve when omeprazole was discontinued. Concomitant medications included acyclovir, Mag-Ox, prednisone, Procardia, Ativan, Zantac, and Lo/Ovral; her medical history included reflux esophagitis and aplastic anemia for which she was receiving a bone marrow transplant at the time of the report.

Foreign experience: There were two cases of pancreatitis received through AERS. One patient was receiving IV omeprazole; both patients had extensive medical histories and were taking numerous concomitant medications.

6.8 Renal events (n = 5)
U.S. experience-There were two cases. A 12-year-old boy developed an increase in creatinine (from 0.5 to 1.7) and an increase in blood urea nitrogen (BUN) (to 24 [baseline not reported]) after taking 20 mg of omeprazole a day for one week; the patient had Sanfilippi's syndrome, diabetes insipidus, hyponatremia, and acute urinary retention. Omeprazole therapy continued and his BUN and creatinine returned to normal. A 10-month-old boy developed nephrotic syndrome after taking 20 mg of omeprazole a day for one month; little information was provided other than the history of cystic fibrosis.

Foreign experience-One case of a patient with acute renal failure with hematuria and interstitial nephritis was received through AERS. Two patients in end stage renal failure received omeprazole and eventually died; both both patients received concomitant medications that were considered suspect by the reporter. One of those patients was receiving IV omeprazole.

6.9 Special senses (n = 4)
U.S. experience- A 6-year-old boy developed tinnitus and hearing loss soon after taking 5 mg of omeprazole a day to treat a stomach ulcer; eight months later the patient underwent an audiogram which revealed a significant drop in the high frequency range.

Foreign experience-There were two cases of blindness (one patient had optic neuritis and the other patient was receiving IV omeprazole) and one case of blurred vision received through AERS. The patient receiving IV omeprazole died (note that this case has been discussed under renal events as well).

6.10 Miscellaneous pediatric events (n = 5)
U.S. experience-There were two cases. A 12-year-old girl experienced diarrhea, rash, headache, backache, stomachache, tightening of the throat, and wheezing after taking 20 mg of omeprazole a day for 16 days. The patient had developed stridor and "noisy breathing" following an influenza-like illness. Omeprazole was stopped and the patient was reported as doing very well. Her medical history included GERD and depressive disorder; concomitant medications were not reported. A 7-year-old boy experienced metabolic acidosis after receiving 20 mg of omeprazole a day (duration unknown); his outcome was not reported. His medical history included partial epilepsy and changes in mental status; concomitant medication included phenytoin.

Foreign experience-There was one case of a polymyositis-like reaction, one case of a dermatomyositis-type reaction, and one case of angioedema and oral thrush reported through AERS.

6.11 Summary of pediatric events
The omeprazole labeling states that safety and effectiveness in children has not been established. The use of omeprazole in children represents less that 3% of total use. None of the pediatric reports received through AERS were particularly compelling. In general, most the pediatric patients described in this section had underlying conditions or were receiving concomitant medications making it difficult relate their outcome to omeprazole use. Further, the types of notable events were consistent with those of concern in adults (i.e. pancreatitis, liver events, hematologic events, drug interactions). Neurological events was the most frequent adverse reaction group; it appears that four patients had an interaction between omeprazole and their seizure medication and one patient was diagnosed with rolandic epilepsy.

7.0 DRUG INTERACTIONS

Omeprazole is metabolized by the cytochrome P-450 system. It is a substrate for isoenzymes 2C8, 2C18, and 2C19; an inhibitor of isoenzymes 2C8, 2C19, and 3A4; and an inducer for isoenzyme 1A2 (American College of Clinical Pharmacy [website=www.accp.com]). Therefore, omeprazole has the potential to interact with other medications also affected by these systems. The labeling states that omeprazole can prolong elimination of diazepam, warfarin, and phenytoin and that clinical reports have been received regarding interactions with cyclosporine, disulfiram, and benzodiazepines.

The Adverse Event Reporting System (AERS) was searched as of March 31, 2000 using omeprazole as suspect and concomitant drug and *Drug interactions* as the MEDDRA PT term. The search produced a total of 209 reports. The individual cases were reviewed for those drugs that had five or more reports (i.e., digoxin, sertraline, divalproex sodium, conjugated estrogens, and fluconazole). Warfarin and cisapride had more than five reports, but they were excluded from this review because an interaction with warfarin is listed in the omeprazole labeling and cisapride has been withdrawn from the market.

A hands-on review of the reports for the drugs mentioned above found a signal of an interaction involving decreased effectiveness of conjugated estrogens (eight cases) when given concomitantly with omeprazole. There were eight cases of a return of menopausal symptoms (e.g., breast tenderness, hot flashes, breakthrough bleeding, uterine bleeding, and increased night sweats) when omeprazole and conjugated estrogens were given concomitantly. Eight reports, however, may not be enough to indicate a definite interaction. Additionally, a possible interaction involving decreased effectiveness of sertraline and divalproex sodium was noted when given concomitantly with omeprazole (three cases reported for each drug).

8.0 SERIOUS HEMATOLOGIC EVENTS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Marrow depression and hypoplastic anemias* and *agranulocytosis* as the MedDRA HLT and PT terms, respectively. The search produced 172 cases. These 172 cases were separated into domestic and foreign and checked for duplicates; only severe hematologic events (i.e., agranulocytosis, aplastic anemia, bone marrow suppression, pancytopenia, severe neutropenia [neutrophil count < 500]) were included for discussion. A total of 16 cases (5 domestic and 11 foreign) were excluded because they were nonserious hematologic events; the remaining 21 reports were duplicates. Thus, there were 47 domestic cases and 88 foreign cases available for review.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 47)

AGE (YEARS):	RANGE 17 to 85, MEAN 62 (n = 38)
SEX:	M (22), F (18), UK (7)
REPORTING YEAR:	1989 (1), 1990 (6), 1991 (4), 1992 (1), 1993 (8), 1994 (3), 1995 (2), 1996 (11), 1997 (2), 1998 (5), 1999 (3), UK (1)
REACTION ONSET (DAYS):	RANGE 4 to 1440, MEAN 142, MEDIAN 30 (n = 21)
DOSE PER DAY (MG):	20 MWF (1), 20 (28), 40 (4), 80 (1), 120 (1), UK (12)
DECHALLENGE POSITIVE:	17
RECHALLENGE POSITIVE:	1
OUTCOME*:	DIED(4), HOSP(25), LIFE-THREATENING(8), NONSERIOUS (4), OTHER (3), UK (9)
EVENT DESCRIPTION:	AGRANULOCYTOSIS (11), PANCYTOPENIA (24), APLASTIC ANEMIA (1), BONE MARROW SUPRESSION (6), MULTIPLE HEMATOLOGIC EVENTS (5)
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEMATOL. EVENTS†	27

* Some patients had multiple outcomes.

† Concomitant medications including allopurinol, amitryptyline, atenolol, captopril, carbamazepine, ceftazidine, cyclosporin, diclofenac, diltiazem, fluconazole, furosemide, isorsorbide, mesalamine, metoclopramide, metoprolol, metronidazole, nortriptyline, prochlorperazine, ranitidine, tobramycin, and vancomycin.

In addition to the Domestic cases that were individually reviewed, there were 88 foreign cases of serious hematologic events in AERS (agranulocytosis [37], pancytopenia [24], aplastic anemia [8], bone marrow supression [8], multiple hematologic events [11]).

Representative Case of Serious Hematologic Event

Case# 4735645 (direct report) [redacted], 1990) A 69-year-old female developed pancytopenia and eventually died after taking 20 mg of omeprazole a day for 16 days to treat reflux esophagitis unresponsive to ranitidine. The patient had been admitted to the hospital for inflammatory bowel disease; her medical history included surgery for lower GI bleeding and adult respiratory distress syndrome. Her lab values after 14 days of omeprazole therapy were reported as follows: WBC 400; Hgb/Hct 10.1/30.1 mg%; and platelets 80,000/mm^3. She developed cellulitis with generalized septicemia and died of bacterial endocarditis 33 days after omeprazole was discontinued. Concomitant medications included corticosteroids, Flagyl, Pamelor, Rowasa, and TPN; she also received a blood transfusion. The reporter stated that her WBC did increase after omeprazole was discontinued.

8.1 Summary of Serious Hematologic Events

This section describes cases of serious hematologic events associated with the use of omeprazole. Pancytopenia (rare) and agranulocytosis (some fatal) are labeled events. Of the four domestic deaths, three patients were receiving medications known to cause hematologic events (one of those patients was taking an 80-mg dose of omeprazole per day) and the fourth patient had a history of bone marrow suppression while taking indomethacin. Overall, more than half (27 out of 47) of the patients were receiving medications know to cause hematologic events. Many reports described in this section lacked specific information (e.g., concomitant medications, lab values) making it difficult to determine causality or severity.

9.0 SERIOUS LIVER EVENTS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Hepatic disorders (exc neoplasms)* and *Liver transplant* as the MedDRA HLGT and PT terms, respectively. Domestic and foreign cases were searched separately. The search produced 208 domestic cases. These 208 cases were separated and checked for duplicates; only unduplicated cases with a serious outcome (i.e., death, life threatening, hospitalization, and disability) were included in this discussion (a total of 57 unduplicated domestic cases).

DEMOGRAPHIC DATA OF SERIOUS DOMESTIC CASES (n = 57)

AGE (YEARS):	RANGE 21 to 90, MEAN 59 (n = 45)
SEX:	M (23), F (28), UK (6)
REPORTING YEAR:	1989 (2), 1990 (10), 1991 (4), 1992 (9), 1993 (3), 1994 (6), 1995 (7), 1996 (5), 1997 (3), 1998 (6), 1999 (2)
REACTION ONSET (DAYS):	RANGE 1 to 730, MEAN 47, MEDIAN 15.5 (n = 36)
DOSE PER DAY (MG):	20 MG (35), 40 mg (5), 60 mg (1), 20-40 MG QOD (1), 20 INC. TO 40 MG (1), 20 mg QOD (1), UK (12)
DECHALLENGE POSITIVE:	25
RECHALLENGE POSITIVE:	1
OUTCOME:	DIED (8), LIFE-THREATENING (8), HOSP (40)*, DISABILITY (1)
EVENT DESCRIPTION:	HEPATITIS (14), HEPATIC FAILURE (16), JAUNDICE (14), MIXED EVENTS (HEPATOCELLULAR AND CHOLESTATIC) (13)
HISTORY OF ALCOHOL ABUSE	4
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE HEPATIC EVENTS†	24

* Two patients required liver transplants.

† Concomitant medications included acetaminophen, allopurinol, amitriptyline, ciprofloxacin, cisapride, clonidine, conjugated estrogen, Darvocet N, Diflucan, Dyazide, diltiazem, enalapril, famotidine, halogenated anesthesia, Hyzaar, Naprosyn, nifedipine, Noroxin, Pravachol, quinapril, ranitidine, steroids, thorazine, Vasotec, verapamil.

In addition to the domestic cases that were individually reviewed, there were 199 foreign cases. A hands-on review and a check for duplicates of the foreign cases was not performed; a report of MEDDRA SOC and PT terms was printed and reviewed. The following counts of serious events were noted: hepatic failure (25), hepatic necrosis (11), hepatitis (all types) (41), cholestatic jaundice (25), and jaundice (33).

Representative Case of Liver Failure

Case# 3387227 (Mfr# 199910200349) — 1999) A 42-year-old female experienced acute liver failure requiring a liver transplant after taking 20 of omeprazole a day for approximately 3 months to treat GERD. The patient had had prior exposure to omeprazole (dose and duration unknown). She developed pruritus, anorexia, and jaundice with elevated SGOT (2165 Units/L), billirubin (10 mg/dL), and alkaline phosphatase (292 Units/L); an HIDA scan of the liver revealed poor uptake and a biopsy indicated massive hepatic necrosis with proliferation of cholangioles. There was no indication of autoimmune hepatitis; hepatitis A and B and herpes virus screens were negative. Her condition deteriorated; she developed Grade I-II hepatic encephalopathy and asterixis. The patient underwent a liver transplant and made an uneventful recovery. Her medical history included hypothyroidism; concomitant medication included Synthroid.

9.1 Summary of Serious Liver Events

This section describes cases of hepatic events possibly associated with the use of omeprazole. The hepatic events discussed in this section are labeled events. The categories in Event Description section above are mutually exclusive (e.g., a case of hepatitis leading to liver failure would be recorded as liver failure). Overall, these cases are more compelling (regarding severity and association with omeprazole) than the cases for other events described in this document. Of the eight deaths, five of the patients were receiving medications known to cause liver events and/or had underlying conditions (including alcohol abuse) that were more likely the cause of death. Two patients required a liver transplant; one case is described above and the other case did not provide much information, but the reporter did state that there was no cause for the patient's hepatitis other than omeprazole use. Four patients developed encephalopathy and four patients had hepatic necrosis. Overall, 24 patients (out of a total of 57 patients) were receiving medications also known to cause liver events; 4 patients had a history of alcohol abuse.

10.0 STEVENS-JOHNSON SYNDROME / TOXIC EPIDERMAL NECROLYSIS

Previously, HFD-180 received a Monitored Adverse Reaction Report concerning severe skin reactions associated with omeprazole dated October 19, 1992, which presented two cases of Stevens-Johnson Syndrome (SJS) and three cases of toxic epidermal necrolysis (TEN) (Attachment B). This section updates that previous information.

AERS was searched for reports of SJS or TEN (MedDRA preferred terms [PT] STEVENS JOHNSON SYNDROME and EPIDERMAL NECROLYSIS) involving omeprazole that were received by the FDA from October 1, 1992 up through and including March 31, 2000. A total of 84 reports were retrieved, which represented 49 unduplicated cases. Forty-two of these cases were from foreign sources, primarily Germany (25), which is performing an extensive epidemiological study regarding severe skin reactions and maintains a registry of patients.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 7)

AGE (YEARS) (n = 6):	Range—47 to 72 years; Median—53 years; Mean—55.7
SEX (n = 6):	Female—2; Male—4
EVENT DATE:	1993, 1995, 1996—1 each; 1997—2; 1998—1; Unknown—1
REACTION ONSET (DAYS) (n=4):	Range—1.5 to 120 (approx.) days; Median—23.5 days; Mean—42.1 days (approx.)
DOSE PER DAY (n = 6):	20 mg—5; 40 mg—1
DECHALLANGE:	Positive—5; Negative—1; Unknown—1
OUTCOME:	Hospitalized—2; Non-serious—4; Unknown—1
REACTION (n = 6):	SJS—4; TEN—1; SJS/TEN—1

Two of the cases had very minimal information; one noting that the patient was admitted to the hospital with "Stevens-Johnson like syndrome," and the other, from a physician reporter, stating the patient came to his office saying "a combination of Prilosec and Dilantin caused Steven-Johnson syndrome." One case had a negative dechallenge in that the patient's rash continued to wax and wane for several weeks following discontinuation of the drug. Also in this case, a confirmed diagnosis was never made; the patient claimed he possibly had a mild case of TEN. There was a well-documented case of TEN, but it's possible that ranitidine, which lists erythema multiforme in its labeling, may have contributed to the reaction. In that case, the patient originally developed a rash while on omeprazole, which was then discontinued and replaced with ranitidine. The rash initially improved, but then progressed after about three weeks of ranitidine therapy, eventually developing into TEN.

Representative case of Stevens Johnson Syndrome

Case# 3300119 (Mfr.# 19980900019) A 47-year-old female with reflux esophagitis, esophageal stricture and hiatal hernia was placed on omeprazole 20 mg twice a day on August 14, 1998 for the treatment of gastroesophageal reflux disease. Concomitant therapy included loratidine and levothyroxine. Five days later, the patient experienced pruritis, which was worse on the hands. Four days after that, the rash had worsened and the patient discontinued omeprazole. Two days later, her physician noted that there were multiple wheel-like bulls-eye lesions on the posterior and anterior aspect of the trunk. There was involvement, to a lesser extent, on the patient's extremities. Additionally, there were several superficially ulcerated areas on her tongue. There was some ecchymotic involvement on the soft palate and some erythematous areas on the posterior pharynx. The patient was diagnosed with probable Stevens-Johnson syndrome. The patient was treated with hydroxyzine, prednisone, and triazolam. Ranitidine was also started for the treatment of reflux. The patient had improved five days after beginning treatment. The rash changed from primarily papular and vesicular to macular, especially on her back and chest, and these areas had begun to scale. There was no further involvement of the oral mucosa and her lips were less swollen.

10.1 Summary of SJS and TEN Cases

One or two domestic cases per year have been reported since the previous document was issued. Of the seven updated domestic cases, three could be considered compelling for an association between the events and omeprazole. None of these cases were fatal. Additionally, there does not appear to be an increase in the reporting of this event since the last consult. The current labeling includes TEN and SJS, noting that some reactions have been severe and fatal.

11.0 VENTRICULAR ARRHYTHMIAS

AERS was searched for reports of ventricular arrhythmias associated with the use of omeprazole that were received by the FDA up through and including March 31, 2000 using the OPDRA Reaction Group VENT ARRHYTHMIAS. This grouping includes the terms VENTRICULAR ARRHYTHMIAS AND CARDIAC ARREST (HLGT), ELECTROCARDIOGRAM QT PROLONGED (PT), ELECTROCARDIOGRAM QT CORRECTED INTERVAL PROLONGED (PT), and ELECTROCARDIOGRAM QRS COMPLEX PROLONGED (PT). A total of 92 reports were retrieved, which represented 76 unduplicated cases. From these 76 cases, 1 was excluded because it involved a report of a medication error in which the patient received Prozac instead of Prilosec. An additional 16 cases were excluded after reviewing them as the association with omeprazole was poor (negative dechallenge, poor temporal relationship, other causes). Three cases, all of them deaths, were not included in the demographics as ventricular arrhythmias per se were not documented, although the deaths were stated as due to cardiac arrest or possible cardiac arrest. Two of those cases involved the use of cisapride and the other one involved the use of amitriptyline, which are all metabolized through the cytochrome P450 system. There were 32 foreign cases in the AERS database. The remaining 24 domestic cases are summarized below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 24)

AGE (n = 18):	Range—7 to 71 years; Median—49.5 years; Mean—48.1 years
SEX (n = 20):	Female—11; Male—9
EVENT DATE:	1990, 92, 93, 94, 95—1 each; 1996—4; 1997—4; 1998—4; 1999—1; Unknown—6
REACTION ONSET (n=9):	Range- 1-60 days; Median-9; Mean 19
DOSE PER DAY (n = 15):	20 mg—12; 40 mg—2; 60mg—1
DECHALLANGE:	Positive—7; Unknown—17
OUTCOME:	Death—5; Hospitalized (or prolonged)—8; Non-serious—7; Unknown—4
REACTION:	Prolonged QT interval—8 PVCs—5 Torsade de pointes—4 Ventricular tachycardia—4 Ventricular fibrillation—4 Palpitations—3 Paroxysmal atrial tachycardia—1 Ventricular bigeminy—1

he reaction total is greater than 24 as some cases listed more than one event.

Regarding onset of event, five of the nine cases involved a potential drug interaction; onset was calculated in relationship to omeprazole initiation. In one of the cases, the patient had been on the drug for 13 months, but experienced the event 4 days after the dose was increased from 20 mg once to 20 mg twice daily. At the same time, the cisapride dose was increased from 30 mg to 40 mg daily (in this case onset was counted as 4 days). In another case, the patient had been taking the drug for 49 days when symptoms appeared (palpitations/syncope); at day 62 of therapy an ECG showed PVCs (in this case onset was counted as 49 days).

Eleven of the 24 cases were potentially due to a drug interaction. Cisapride was involved in six of these cases. Of the four torsade de pointes cases, three included the concomitant use of cisapride. Other potential drug interactions included amiodarone, terfenadine, nelfinavir, clarithromycin, and nicardipine.

Representative Case: Prolongation of QT interval

Case# 3152050 USA
A 55-year-old male with a history of a kidney transplant and CAD, was admitted to the hospital on 9/25/98 already on cisapride 10 mg four times a day for chest pain. On 9/26 the patient was started on omeprazole 20 mg once a day for symptoms of GERD. Baseline ECG on 9/25 showed a QT interval of 400 msec. After receiving three doses of omeprazole the QT interval on 9/28 was 500 msec. Omeprazole was stopped and replaced with famotidine. On 9/30 the QT interval was back to baseline at 380 msec.

11.1 Summary of Ventricular Arrhythmia Cases

Of the 16 cases involving a serious arrhythmia (increased QT interval, torsade de pointes, ventricular fibrillation, ventricular tachycardia), 11 were potentially due to a drug interaction, principally with cisapride (6). Of the 13 cases in which there was no interacting drug mentioned, 8 were non-serious arrhythmias including PVCs, palpitations, ventricular bigeminy, and paroxysmal atrial tachycardia. It appears omeprazole has the potential for causing certain arrhythmias (tachycardia, bradycardia, and palpitation are listed in the product labeling). The risk for serious arrhythmias may be increased when used with interacting drugs that are known to produce such arrhythmias (e.g., cisapride). However, the data from AERS is not supportive of a clear relationship of omeprazole independently to cause such serious ventricular arrhythmias, and cisapride is no longer available on the general market.

12.0 PANCREATITIS

AERS was searched as of March 31, 2000 using omeprazole as suspect drug and *Pancreatitis* and *Digestive enzymes* as the MedDRA HLT terms. The search produced 126 cases. These 126 cases were separated into domestic and foreign and checked for duplicates. A total of 3 cases were excluded because they were miscoded and 34 reports were duplicates. Thus, there were 62 unduplicated domestic cases and 27 unduplicated foreign cases for review.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 62)

AGE (YEARS):	RANGE 3 TO 85, MEAN 52 (n = 46)
SEX:	M (29), F (26), UK (7)
REPORTING YEAR:	1989 (1), 1991 (5), 1992 (2), 1994 (1), 1995 (6), 1996 (11), 1997 (15), 1998 (14), 1999 (3), 2000 (1), UK (3)
REACTION ONSET (DAYS):	RANGE 2 TO 540, MEAN 131, MEDIAN 51
DOSE PER DAY (MG):	10 (1), 20 (47), 40 (1), 60 (1), 20 QOD (1), UK (11)
DECHALLENGE POSITIVE:	24
RECHALLENGE POSITIVE:	2
OUTCOME*:	DIED (2), HOSP (41), NONSERIOUS (12), LIFE-THREATENING (3), RECOVERED (1), UK (5)
EVENT DESCRIPTION:	PANREATITIS (58), ELEVATED AMYLASE AND/OR LIPASE (4)†
PTS WITH HISTORY OF ALCOHOL ABUSE	3
PTS TAKING CONCOMITANT MEDS KNOWN TO CAUSE PANCREATIC EVENTS‡	13

* Several patients had multiple outcomes.
† Two of these patients had clinical symptoms of pancreatitis as well as elevated amylase and/or lipase, but reporter did not specify that the patient had pancreatitis.
‡ Concomitant medications including furosemide, lisinopril, prednisone, divalprox, estrogens, Prozac, Voltaren XR, Zestril, valproic acid, and Procardia.

In addition to the Domestic cases that were individually reviewed, there were 27 foreign cases of pancreatitis in AERS; 7 of those cases resulted in death from other causes. (Note that four patients were receiving IV omeprazole.)

Representative Case of Pancreatitis

Case# 4733766 (Mfr# [redacted] 90070191) — 1990) A male (age unknown) developed an ileus one week after taking an unknown dose of omeprazole to treat duodenal ulcer; he subsequently developed pancreatitis, underwent surgery, and eventually died. His medical history included thrombocytopenia; concomitant medications included Augmentin, Lasix, and unspecified steroids.

12.1 Summary of Pancreatitis Cases

This section describes 62 cases of pancreatitis possibly associated with the use of omeprazole. Pancreatitis (some fatal) is a labeled event. Two domestic deaths were reported; one case is described above and the other case provided even less information. Eight patients were reported to have acute pancreatitis (including one of the patients that died) and one patient was reported to have hemorrhagic pancreatitis. Of these nine cases, three patients were receiving concomitant medications known to cause pancreatitis, two patients had a history of pancreatic problems, one patient had a history of alcohol abuse, and one patient's pancreatitis was attributed (by the physician) to gallstones. Overall, 13 of the 62 patients were receiving medications known to cause pancreatitis, 3 patients had a history of alcohol abuse, and 4 patients had a history of pancreatic problems. Many reports described in this section lacked relevant information (e.g., concomitant medications, lab values) making it difficult to assess causality or severity.

13.0 OPHTHALMOLOGIC EVENTS

This section also responds to a consult dated February 17, 2000 from HFD-180 for a search of the AERS database for cases of visual disturbances associated with the use of omeprazole. The purpose of that request was to provide documentation for the addition of "blurred vision" and "eye irritation" to the Adverse Reactions section of the omeprazole labeling, as requested by the manufacturer.

Note that three previous consults have been completed at HFD-180's request regarding this issue (see Attachments C, D, and E). The case inclusion date for the most recent consult (Attachment E) was April 28, 1998. The reader is encouraged to review these previous documents.

To update the previous consults, AERS was searched using omeprazole as suspect drug and *Eye Disorders* as the MedDRA System Organ Class (SOC) term. This search produced a total of 351 reports. A listing of the eye events with 10 or more cases is presented below (some of these numbers may represent duplicate reporting). In order to evaluate the most severe outcome of an ophthalmic event, a second search using omeprazole as suspect drug and *Blindness HLT* as the MedDRA High Level Term (HLT) was performed from the time of marketing to March 31, 2000. This search produced a total of 31 reports. There were 11 domestic blindness cases; a hands-on review of these was conducted.

SOC EYE DISORDERS: EVENTS WITH 10 OR MORE CASES (U.S. PLUS FOREIGN)

Vision abnormal NEC	63
Vision blurred	40
Dry eye NEC	28
Eye disorder NOS	20
Visual distrubance	20
Visual acuity reduced	17
Eye pain	15
Diplopia	15
Papilledema	14
Optic atrophy	13

DEMOGRAPHIC DATA FOR U.S. BLINDNESS CASES (n = 11)

AGE (YEARS):	66 MEAN (RANGE 39 to 81)
SEX:	M (2), F (9)
YEAR OF EVENT:	1989 (1), 1993 (1), 1994 (2), 1997 (5), 1998 (2)
REACTION ONSET:	1 DOSE (2), 2 DAYS (1), 8 DAYS (1), 38 DAYS (1), >1.5 YEARS (3), UK (3)
ORAL DOSE PER DAY:	20 MG (7), 20-40MG (1), 40MG (1), UK (2)
DECHALLENGE:	POSITIVE (1), NEGATIVE (1)
RECHALLENGE:	POSITIVE (1)

SERIOUS OUTCOME RELATED TO OPHTHAL. EVENT: HOSPITALIZED (2), DISABLED (4)

The following three blindness cases are domestic cases received since the last consult of April 23, 1998

Case# 3300292 (Mfr# 19980600094) (U.S. [consumer], 1998) A 61-year-old female was driving and became unable to see out of her left eye after taking omeprazole 20 mg for one day to treat "reflux." She also experienced dizziness. Her blindness abated (timeframe unknown); she continued omeprazole therapy. Her concomitant medications and medical conditions were not reported.

Case# 3130343 (Mfr# 19980500646) 1997) A 68-year-old female experienced temporary loss of vision lasting for several minutes after taking one dose of omeprazole 20 mg to treat GERD and *Helicobacter pylori*. Omeprazole was discontinued and the event abated. Concomitant medications included Lasix, Zestril, Coumadin, and Lanoxin; she also received Biaxin and Tritec, but temporal relationship to omeprazole therapy was not specified. Her medical history included chronic atrial fibrillation, hypertension, other disorders of the esophagus, and allergy to Naprosyn (caused rash).

Case# 3295045 (Mfr# 19980300172) reported 1998) An 81-year-old female developed blindness after taking omeprazole 20 mg every 2 to 3 days for "several years" to treat GERD. The event abated after omeprazole was discontinued. Her medical history included macular degeneration; muscle spasm reaction to cimetidine; visual difficulties from lansoprazole, cisapride, and famotidine; and allergies to sulfa, penicillin, neosporin, and novacaine. Concomitant medications included Prevacid, Propulsid, and Pepcid.

13.1 Summary of Ophthalmologic Events

This information updates three previous consults regarding omeprazole and ophthalmic events. OPDRA was asked specifically about AERS cases of blurred vision and eye irritation, as these relate to a manufacturer's request for labeling change. In addition, we looked at cases of blindness received through AERS since the time of marketing. From the recent printout of all visual disturbances associated with omeprazole use, there are a total of 40 reports of *Vision blurred*. There are a total of 5 reports of *Eye irritation NOS* in AERS. Note that eye irritation also could include other PT terms such as *Eye Pain* (15 cases), *Eye inflammation* (1 case), *Dry eye NEC* (28 cases), *Conjunctivitis NEC* (18 cases), as well as other terms. It appears that we continue to receive AERS reports of blurred vision, eye irritation and other ophthalmologic events associated with the use of omeprazole. However, it is difficult to establish a clear relationship between omeprazole use and these events, particularly because of the extensive use of omeprazole in the U.S. as well as the prevalence of general vision disorders.

It would appear reasonable to allow the sponsor to include blurred vision and eye irritation in the omeprazole labeling, although the relationship appears inconclusive. A general term, such as "visual distrubance" or "abnormal vision" might also be considered to reflect the reporting of such cases (Vision abnormal NEC: 63 cases, Visual distrubance: 20 cases, Visual acuity reduced: 17 cases). Although blindness cases have been reported, analysis of these do not support a relationship to omeprazole; no labeling recommendation regarding blindness can be made at this time.

14.0 HEARING DISORDERS

AERS was searched for reports of hearing disorders associated with the use of omeprazole that were received by the FDA up through and including March 31, 2000. Terms used for the search were HEARING DISORDERS (HLGT), INNER EAR & VIIIth CRANIAL NERVE DISORDERS (HLGT), and MISCELLANEOUS EAR DISORDERS (HLGT). A total of 167 reports were retrieved, which represented 158 unduplicated cases. Twenty-six cases were excluded after reviewing them as the association with omeprazole was poor (poor temporal relationship, other causes [e.g., salicylate intoxication, acoustic neuroma, earwax]). There were 22 foreign cases in the AERS database. The remaining 110 domestic cases are summarized below.

DEMOGRAPHIC DATA OF DOMESTIC CASES (n = 110)

AGE (n = 83):	Range—6 to 89 years; Median—54 years; Mean—54.6 years
SEX (n = 100):	Female—64; Male—36
EVENT DATE (n = 76):	1989—2 1995—9 1990—5 1996—9 1991—4 1997—15 1992—1 1998—17 1993—10 1999—2 1994—2
REACTION ONSET (n = 57):	Range—1 day to approx. 3.5 years; Median—approx. 6 days; Mean—approx. 100.6 days
DOSE PER DAY (n = 70):	5 mg—1; 20 mg—54; 40 mg—15
DECHALLANGE/RECHALLENGE:	Dechallenge positive—49 Dechallenge negative—16 Rechallenge positive—6 Rechallenge negative—1
OUTCOME:	Non-serious—100; Disability—5; Hospitalized—1; Unknown—4
REACTION:	Tinnitus—68 Vertigo—21 Hearing loss—17 Dizziness—14 Ear pain—10 "Ototoxicity" (undefined)—2

The reaction total is greater than 110 as some cases listed more than one event.

A review of the cases of ***hearing loss*** (n = 17) showed the following demographics:

AGE (n = 15):	Range—6 to 74 years; Median—49 years; Mean—47.3 years
SEX (n = 17):	Female—8; Male—9

REACTION ONSET (n = 11):	Range—1 day to approx. 6.5 months; Median—approx. 5 days; Mean—approx. 25.4 days
DOSE PER DAY (n = 10):	5 mg—1; 20 mg—7; 40 mg—2
DECHALLENGE:	Dechallenge positive—11 Dechallenge negative—3
OUTCOME (n = 15):	Non-serious—11; Disability—3; Required intervention (Rx)—1

Representative Case of Hearing Loss

Case# 5499583; Mfr.# 19950900131 (USA, 1995) A 42-year-old male physician with no known allergies was placed on omeprazole 20 mg daily for the treatment of GERD on 09/09/95. There were no concomitant medications reported. On 09/16/95 the patient experienced decreased auditory acuity. Audiometric exam revealed a unilateral sensory deficit, and an MRI was negative. Omeprazole was discontinued on 09/16/95 and since that time his hearing has improved slightly.

There did not appear to be an appreciable difference in the characteristics of the patients who developed HL compared to the group as a whole, although they tended to be younger in age. The majority of HL cases (65%) exhibited a positive dechallenge with the patient either returning to baseline or showing an improvement in symptoms.

An attempt was made to determine from all cases with a negative dechallenge (n = 16), which might indicate a permanent hearing disorder, if they could be associated with a longer duration of therapy. In those negative dechallenge cases in which a reaction onset could be determined (n = 7), the median time to onset was 72 days with a mean of 108.4 days, which could imply that a longer duration of therapy may lead to permanent damage, although additional follow-up in those patients might prove otherwise. On the other hand, in the four patients who had a reaction after years of therapy (two cases of tinnitus, one case each of vertigo and ear pain), three had a positive dechallenge (unknown for one case of tinnitus). In the three patients with HL who had a negative dechallenge, there was not enough information to make a determination regarding length of therapy and permanent HL. Two of these patients were considered to have a permanent disability, which occurred after approximately six weeks and six and a half months of therapy, respectively. The third patient's condition was described as persisting 10 days following discontinuation of omeprazole, which he had taken for approximately 9 days. In those HL patients with a positive dechallenge, reaction onset ranged from one to seven days following initiation of therapy. Therefore, in cases of hearing loss, it might appear that a longer duration of therapy may lead to permanent damage, but this is a tenuous assumption based on only two cases.

14.1 Summary of Hearing Disorder Events

Regarding the 110 domestic cases, the vast majority (91%) had a non-serious outcome and in 45% of the cases there was documentation of improvement in the hearing disorder after omeprazole was discontinued (positive dechallenge). Tinnitus and vertigo represented the most frequently submitted reports and both are listed in the product labeling along with dizziness. Hearing loss (HL) and ear pain are not specifically listed in the product labeling and accounted for 17 and 10 reports, respectively. The 17 hearing loss cases were mainly reversible; there was not a strong signal for hearing loss association with omeprazole. Further, an attempt was made to relate duration of omeprazole use to nonreversible hearing disorders by reviewing 17 cases with negative dechallenge. Although a trend was seen with the nonserious cases, only two hearing loss cases seemed to bear this relationship.

15.0 CANCER

A July 30, 1999 memorandum summarized a review of the medical literature and worldwide post-marketing reports for tumors associated with proton pump inhibitors including omeprazole. The medical literature review included a discussion of toxicological studies in rats, mice and dogs that showed generalized hyperplasia of the gastric mucosa. No human studies were identified in the search that proved carcinogenesis. This document also described 362 AERS reports of neoplasms, benign and malignant as of 7/13/99[1]. Among these domestic and foreign cases, age and gender information was available in 276; 45% were female and 39% were considered elderly. The 85 case report forms of domestic and foreign GI neoplasms were retrieved and 54 unduplicated U.S. cases were analyzed; neoplasms reported included gastric polyps (19), gastric cancer (14) and gastric carcinoids (9). This document is included as Attachment F.

15.1 CANCER REPORTS IN AERS

Two updated AERS searches (data as of 3/31/2000) were performed relating to cases of cancer. The first search included the SOC Neoplasms benign and malignant (including cysts and polyps). This broad search revealed a total of 456 cases. Two hundred fifteen (215) were domestic, 236 were foreign and in 77 reporter country was unknown. Neoplasm events of any nature among the 456 cases which had counts of 5 or more are presented below (some may be duplicates):

Neoplasm NOS	54
Gastrointestinal tract cancer NOS	40
Carcinoma NOS	20
Gastric polyps	16
Gastrointestinal neoplasm NOS	12
Carcinoid tumor of the stomach	10
Lymphoma NOS	8
Carcinoid tumor NOS	6
Cyst NOS	5

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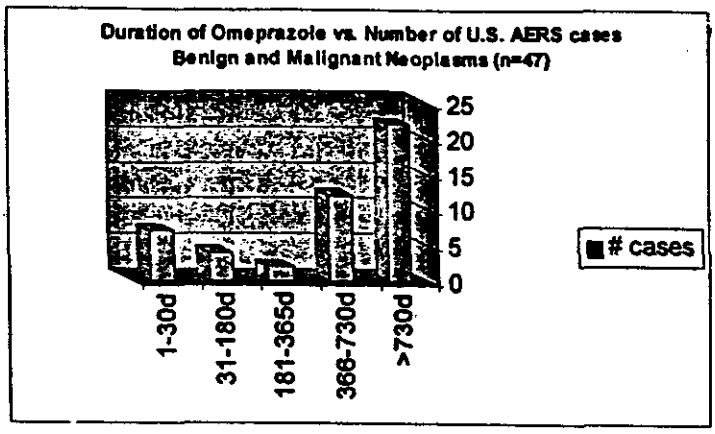
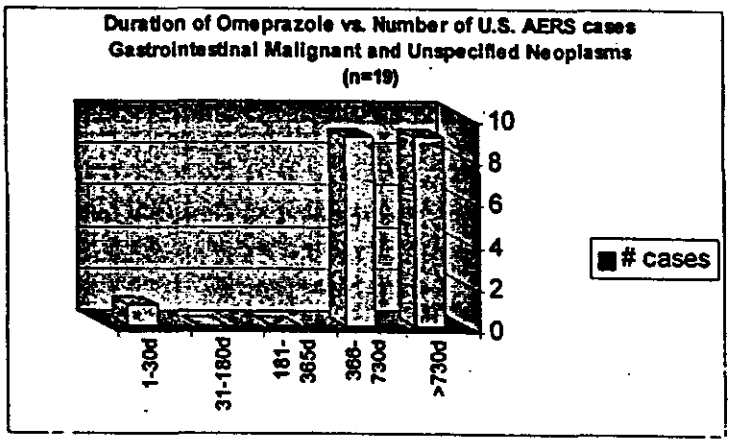
The second search utilized the HLGT Gastrointestinal neoplasms malignant and unspecified, which revealed 171 cases, 78 of which were from the U.S. (domestic). The domestic cases of all cancers and gastrointestinal cancers were further analyzed to relate duration of use to numbers of reported cases of cancer. Duration was a computer-based calculation, which used the following algorithm:

Number of days duration = Start Date of omeprazole to End Date of omeprazole (if no End Date was present, Event Start Date was utilized).

Since this calculation depended on the specific data fields being populated in the reports, this did not result in a large data set. Of the 215 total domestic cases, 47 had sufficient data; of the 78 total GI cases, only 19 had sufficient data to perform the duration calculation. The results are presented graphically below. There is a general trend for larger numbers of reports with a longer duration of use, however, conclusions would be difficult to draw as this data is derived from small numbers from a spontaneous reporting system, which is subject to various reporting biases.

[1] Correction of previous document information: total number of AERS reports for omeprazole as of 7/13/99 was approximately 8400; number of U.S. cases of neoplasms (all types) was approximately 180. These numbers may include duplicate reporting.





15.2 CANCER DATA IN THE LITERATURE

An updated review of the literature was obtained June 2000 to look for case reports of cancer or incidence studies of Omeprazole-related cancer. The following databases were searched: MEDLINE, Embase, Derwent Drug File, IPA, Biosis, Life Sciences, and CANCERLIT. A few possible cases of omeprazole-related cancers were identified in the literature review. A 31-year-old man who had received four courses of antiulcer drugs (famotidine, omeprazole, and lansoprazole) over 38 months developed an argyrophil-positive carcinoid tumor (1). Three patients with severe exudative distal esophagitis were diagnosed with invasive adenocarcinoma within one year of continuous omeprazole treatment (2).

A recent comprehensive review article by Laine et al summarizing animal studies and short- and long-term human studies asserts that omeprazole rarely produces adverse events (3). Since most cancers generally have long latency periods, with gastric cancer reported to have a latency period greater than 15 years (4), a special search for long-term studies was completed to look for cancer incidence. Five long-term (> 12 months of treatment) studies of omeprazole were reviewed (Table 1) (5-9). These studies were conducted outside the United States and may have overlapping patient populations (the methods sections provide limited patient population descriptions). Most of the investigators of these studies also received funding from the sponsor. The longest period of treatment for any study group was 11 years - short of the time needed to study omeprazole-related cancers. No histologically proven gastric cancer cases were reported in any of these studies. Two possible cases of cancers were reported by Lloyd-Davies et al - one patient diagnosed with primary pancreatic and duodenal tumor after an

undefined period of drug exposure and another patient diagnosed with lymph node metastasis without an identified primary tumor and an undefined drug exposure (8). Klinkenberg-Knol et al reported a case of Barrett's carcinoma diagnosed in a 75-year-old man who had a Barrett's ulcer at study entry (9). Six other carcinomas, none of them gastric, were reported in this same study(9).

The long-term studies of omeprazole-related cancer that have been published are limited by three important factors – study size, exposure time, and duration of follow-up. A study of omeprazole-related cancer requires a large number of patients and an extended period of follow-up since gastric cancer is not common, only 22,000 cases of gastric cancer occur in the United States each year (10), and has a long latency period. The studies reviewed have limited number of patients exposed for short time periods and limited follow-ups. The study of omeprazole-related cancer requires extended cohort or nested case control designs that include adjustments for potential confounders, such as underlying disease and smoking. None of the studies in the literature meet this criteria.

Table 1. Summary of Long-term Studies of Omeprazole Cancer Outcomes

Study	No. of Patients	Patient Population	Range of Treatment (No. Range)	Dose	No. of Cancer Cases
Lloyd-Davies KA et al 1988*	80	Zollinger-Ellison	< 1 month – 4 yrs; mean 19 months	260 - 360 mg (median 60 – 70 mg)	1 - Pancreatic and duodenal carcinoma 1 – lymph node metastasis
Joelson S et al 1992*	859	Poorly responsive peptic ulcer or oesphagitis	Up to 6 years	NL	0
Solcia E et al 1992*	448	Peptic ulcer, anastomotic ulcer, or reflux oesophagitis	Up to 4 years	20 - 40 mg	0
Lamberts R et al 1993	74	Chronic esophageal, gastric, or duodenal ulcerations resistant to other treatment	6 months – 7 yrs; median 48 months	40 - 60 mg	0
Klinkenberg -Knol EC et al 2000*	230	Persistent reflux esophagitis	Up to 11 years; mean 6.5 years	10 – 120 mg	1 - Barrett's ca and 6 - non-gastric carcinomas

* Astra Hässle AB either listed as an author or source of funding for the study

16.0 DELAYS IN DIAGNOSIS

Concerns about possible delays in diagnosis exist because the symptoms of gastric cancer can be similar to those of peptic ulcer and thus attempts at medical treatment may be initiated without diagnostic work-ups (11, 12). Diagnostic delays related to cimetidine have been reported in the literature in the past and can be instructive when considering diagnostic delays related to omeprazole. Stoddard et al reviewed the cases of adenocarcinoma of the stomach diagnosed in their unit from August 1979 to May 1980. Investigators identified 12 of 29 patients with delays between 2 and 12 months; 8 of the 12 patients had been treated with cimetidine and antacids for up to 12 months before surgical referral (13). Another group of investigators from the United Kingdom searched the Cambridge Cancer Registration Bureau to identify patients with gastric carcinoma presenting to their hospital between 1978 and 1980 (12). Medical records were reviewed and general practitioners interviewed patients (if necessary) to obtain information about the 100 cases identified. Sixteen patients received cimetidine before diagnosis (duration of therapy varied from 1 to 13 months). Five of the 16 received cimetidine without an upper gastrointestinal barium study or endoscopy.

Mikulin et al more recently interviewed all patients identified with gastric cancer in Nottingham from October 1981 and September 1982 (14). Eighty-three patients (mean age 71 years) were asked about their symptoms and management histories. Fifty-three (64%) of the patients received medication prior to diagnosis, 24 of whom had no investigation prior to drug therapy, 17 of whom received cimetidine. There was no difference in the median days of delay to treatment among those receiving cimetidine (6 weeks) and those receiving antacids (5 weeks).

Of special concern related to drugs used to treat dyspepsia are the case reports of patients who show improvement with drug treatment, delay further diagnostic work-up, and later are identified as patients with gastric cancer. Mikulin et al describes 3 patients who had benign gastric ulcers diagnosed, were treated with cimetidine, and showed improvement of their symptoms (14) All three patients relapsed and were found to have gastric cancer. Wayman et al reports a case series of 7 patients who participated in a special endoscopy protocol (15). Patients in this study had an initial endoscopy, were then started on proton pump inhibitors, and underwent a second endoscopy to ensure resolution of any biopsied ulcer. The 7 patients were found to have ulcerating early gastric cancer when the second endoscopy was performed, but only after inadvertently receiving a short course of a proton pump inhibitor that produced an asymptomatic state. Given the resulting asymptomatic state these patients might have experienced further diagnostic delays if they had not been participated in this study, but instead just initiated medical therapy.

All these papers were conducted by English authors and may not be generalizable to the United States where medical manangement may differ. These papers emphasize, though, that even medical experts have delayed the diagnosis or mis-diagnosed gastric cancer and used a variety of drugs in lieu of or despite a diagnostic work-up. At least one study suggests that the delays in diagnosis were not different for over the counter treatments (antacids) versus prescription treatments (cimetidine) (14). Future studies of delays in diagnosis related to over the counter omeprazole should be done and could use similar methods to these referenced studies.

18.0 DISCUSSION/CONCLUSION

This consult was prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review selected adverse events for omeprazole as the sponsor has submitted an NDA for a change to nonprescription status. The Adverse Event Reporting System (AERS) was searched for adverse event reports received for omeprazole up to March 31, 2000; 10,005 reports were identified in the database. Both domestic and foreign experience is addressed in this document, however, the focus is on the domestic experience. The following issues have been reviewed in this consult: cases with an outcome of death, pediatric experience, drug interactions, serious hematologic events, serious liver events, serious skin disorders, vertricular arrhythmias, pancreatitis, ophthalmologic events, hearing disorders, cancer reports, and delay in diagnosis. For many of these adverse events, analysis of cases did not support significant safety concerns with general use of omeprazole; many patients had underlying conditions or were taking concomitant medications which could have contributed to the events. Summary of these issues appears at the end of each section. The most compelling issue reviewed was serious liver events, which were temporally related to omeprazole use and included serious outcomes such as liver transplants, deaths, and encephalopathy. Serious liver events are included in the current labeling for omeprazole. The pediatric cases reviewed tended to mirror events seen in adults; these typically were not healthy children prior to omeprazole use.

A review of AERS reports for gastrointestinal neoplasms (this body site had the most cancer-related reports in the AERS database) found that there was a trend for larger numbers of reports with a longer duration of omeprazole use, however, conclusions cannot be made because the data was derived from small numbers of spontaneous reports in the system. A review of the studies and case reports in the literature for omeprazole-related cancer revealed that the studies had limited numbers of patients exposed for short time periods with limited follow-ups. A review of the literature for delays in GI cancer diagnosis due to patient self-medication revealed that both prescription and OTC use of antacid drugs may delay diagnosis; additional studies are needed. Data regarding congenital anomalies will be addressed in a separate document.

Given the number of years that omeprazole has been on the market (11 years) and its extensive use ([redacted] prescriptions), AERS report data suggest that the frequency of serious adverse events associated with omeprazole is low, however, with any evaluation of spontaneous reports, underreporting must be considered.

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Attachment A

PT	Count of PTs	Percent of Total	Labeled
Drug Ineffective	692	6.92	U
Abdominal Pain Nos	536	5.36	U
Diarrhoea Nos	491	4.91	U
Headache Nos	489	4.89	U
Dermatitis Nos	450	4.50	U
Nausea	406	4.06	U
Dizziness (Exc Vertigo)	334	3.34	U
Pruritus	323	3.23	U
Drug Interaction Nos	288	2.88	U
Pyrexia	269	2.69	U
Alopecia	249	2.49	U
Condition Aggravated	249	2.49	U
Vomiting Nos	232	2.32	U
Thrombocytopenia	227	2.27	U
Chest Pain	224	2.24	U
Pain Nos	215	2.15	U
Dyspepsia	211	2.11	U
Arthralgia	197	1.97	U
Dyspnoea Nos	194	1.94	U
Urticaria Nos	192	1.92	U
Confusion	189	1.89	U
Constipation	188	1.88	U
Back Pain	185	1.85	U
Asthenia	179	1.79	U
Leucopenia Nos	175	1.75	U
Flatulence	170	1.70	U
Dysalgia	166	1.66	U
Abdominal Pain Upper	161	1.61	U
Paraesthesia Nec	159	1.59	U
Dry Mouth	153	1.53	U
Hepatic Function Abnormal Nos	150	1.50	U
Taste Disturbance	139	1.39	U
Abdominal Distension	137	1.37	U
Insomnia Nec	137	1.37	U
Blood Creatinine Increased	132	1.32	U
Fatigue	128	1.28	U
Malaise	128	1.28	U
Depression Nec	126	1.26	U

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PT	Count of PTs	Percent of Total	Labeled
Cough	120	1.20	U
Weight Increased	120	1.20	U
Gastrointestinal Disorder Nos	117	1.17	U
Liver Function Tests Nos Abnormal	115	1.15	U
Oedema Peripheral	106	1.06	U
Weakness	103	1.03	U
Anaemia Nos	101	1.01	U
Palpitations	100	1.00	U
Tremor Nec	99	0.99	U
Gastrointestinal Tract Cancer Nos	98	0.98	U
Hepatitis Nos	98	0.98	U
Renal Failure Acute	98	0.98	U
Weight Decreased	97	0.97	U
Sedation	93	0.93	U
Dysphagia	92	0.92	U
Pancreatitis Nos	91	0.91	U
Nervousness	90	0.90	U
Tinnitus	90	0.90	U
Hypoaesthesia	88	0.88	U
Muscle Cramps	87	0.87	U
Sepsis Nos	87	0.87	U
Hypertension Nos	85	0.85	U
Anxiety Nec	84	0.84	U
Jaundice Nos	84	0.84	U
Blood Bilirubin Increased	83	0.83	U
Gastrointestinal Haemorrhage Nos	81	0.81	U
Neoplasm Nos	80	0.80	U
Hyponatraemia	78	0.78	U
Urinary Frequency	77	0.77	U
Face Oedema	76	0.76	U
Hallucination Nos	76	0.76	U
Syncope	76	0.76	U
Tachycardia Nos	76	0.76	U
Blood Urea Increased	75	0.75	U
Drug Effect Decreased	74	0.74	U
Hypersensitivity Nos	74	0.74	U
Sweating Increased	74	0.74	U
Pain In Limb	72	0.72	U

PT	Count of PTs	Percent of Total	Labeled
Eructation	71	0.71	U
Pancytopenia	71	0.71	U
Oedema Nos	69	0.69	U
Acute Circulatory Failure	67	0.67	U
Hypoglycaemia Nos	66	0.66	U
Myocardial Infarction	66	0.66	U
Laboratory Test Abnormal Nos	64	0.64	U
Haematuria Present	63	0.63	U
Rash Maculo-Papular	63	0.63	U
Vision Abnormal Nec	63	0.63	U
Agitation	62	0.62	U
Angioneurotic Oedema	62	0.62	U
Agranulocytosis	61	0.61	U
Convulsions Nos	60	0.60	U
Nephritis Nos	60	0.60	U
Pneumonia Nos	60	0.60	U
Oedema Lower Limb	59	0.59	U
Rash Erythematous	58	0.58	U
Coma Nec	57	0.57	U
Epidermal Necrolysis	57	0.57	U
Renal Failure Nos	57	0.57	U
Stevens Johnson Syndrome	57	0.57	U
Haemoglobin Decreased	56	0.56	U
Neutropenia	54	0.54	U
Stomatitis	54	0.54	U
Blister	53	0.53	U
Drug Maladministration	53	0.53	U
Oesophagitis	53	0.53	U
Amnesia Nec	52	0.52	U
Burning Sensation Nos	52	0.52	U
Impotence	52	0.52	U
Blood Alkaline Phosphatase Nos Increased	51	0.51	U
Blood Creatine Phosphokinase Increased	49	0.49	U
Hypotension	49	0.49	U
Iron Deficiency Anaemia	48	0.48	U
Renal Impairment Nos	48	0.48	U
Cerebrovascular Accident Nos	47	0.47	U
Faeces Discoloured	47	0.47	U

PT	Count of PTs	Percent of Total	Labeled
Peripheral Neuropathy Nec	47	0.47	U
Prothrombin Level Decreased	47	0.47	U
Sore Throat Nos	47	0.47	U
Anorexia	46	0.46	U
Aspartate Aminotransferase Increased	46	0.46	U
Hyperglycaemia Nos	46	0.46	U
Gastritis Nos	45	0.45	U
Tongue Oedema	45	0.45	U
Haemolytic Anaemia Nos	44	0.44	U
Jaundice Cholestatic	44	0.44	U
Pharyngitis Nos	44	0.44	U
Alanine Aminotransferase Increased	43	0.43	U
Gastro-Oesophageal Reflux Disease	43	0.43	U
Carcinoma Nos	42	0.42	U
Drug Level Nos Above Therapeutic	42	0.42	U
Erythrocyte Sedimentation Rate Increased	42	0.42	U
Urinary Tract Infection Nos	42	0.42	U
Appetite Decreased	41	0.41	U
Dermatitis Bullous	41	0.41	U
Gynaecomastia	41	0.41	U
Hepatic Failure	41	0.41	U
Cardiac Failure Nos	40	0.40	U
Infection Nos	40	0.40	U
Vision Blurred	40	0.40	U
Ecchymosis	39	0.39	U
Asthma Nos	38	0.38	U
Cardiac Arrest	38	0.38	U
Dehydration	38	0.38	U
Eosinophilia (Exc Pulmonary)	38	0.38	U
Arrhythmia Nos	37	0.37	U
Psychotic Disorder Nos	37	0.37	U
Unevaluable Reaction	37	0.37	U
Hypokalaemia	36	0.36	U
Mouth Ulceration	36	0.36	U
Platelet Count Decreased	36	0.36	U
Vasodilatation	36	0.36	U
Bone Marrow Depression Nos	35	0.35	U
Haematemesis	35	0.35	U

PT	Count of PTs	Percent of Total	Labeled
Haemorrhage Nos	35	0.35	U
Hypertonia	35	0.35	U
Thinking Abnormal Nec	35	0.35	U
Dry Skin	34	0.34	U
Gait Abnormal Nos	34	0.34	U
Urine Abnormal Nos	34	0.34	U
Vertigo Nec	34	0.34	U
Abnormal Dreams	33	0.33	U
Delirium	33	0.33	U
Disorientation	33	0.33	U
Gamma-Glutamyltransferase Increased	33	0.33	U
Photosensitivity Reaction Nos	33	0.33	U
Rigors	33	0.33	U
Bradycardia Nos	32	0.32	U
Hyperkalaemia	32	0.32	U
Leucocytosis Nos	32	0.32	U
Myasthenic Syndrome	32	0.32	U
Deafness Nos	31	0.31	U
Feeling Abnormal	31	0.31	U
Hepatocellular Damage	31	0.31	U
Epistaxis	30	0.30	U
Glossodynia	30	0.30	U
Oral Candidiasis	30	0.30	U
Dermatitis Exfoliative Nos	29	0.29	U
Flushing	29	0.29	U
Purpura Nos	29	0.29	U
Urine Discolouration	29	0.29	U
Acidosis Nos	28	0.28	U
Blood Gastrin Increased	28	0.28	U
Blood Pressure Increased	28	0.28	U
Cholelithiasis	28	0.28	U
Dry Eye Nec	28	0.28	U
Glossitis	28	0.28	U
Throat Irritation	28	0.28	U
Amblyopia Nos	27	0.27	U
Angina Pectoris	27	0.27	U
Antinuclear Factor Positive	27	0.27	U
Aplastic Anaemia	27	0.27	U

PT	Count of PTs	Percent of Total	Labeled
Atrial Fibrillation	27	0.27	U
Dysuria	27	0.27	U
Melaena	27	0.27	U
Nephritis Interstitial	27	0.27	U
Rash Pruritic	27	0.27	U
Urinary Retention	27	0.27	U
Arthritis Nos	26	0.26	U
Blindness Nec	26	0.26	U
Gastric Polyps	26	0.26	U
Muscle Weakness	26	0.26	U
Oesophageal Reflux	26	0.26	U
Vasculitis Nos	26	0.26	U
White Blood Cell Count Decreased	25	0.25	U
Anaphylactic Reaction	24	0.24	U
Blood Lactate Dehydrogenase Increased	24	0.24	U
Encephalopathy Nos	24	0.24	U
Hostility	24	0.24	U
Personality Disorder Nos	24	0.24	U
Apnoea	23	0.23	U
Ataxia Nec	23	0.23	U
Blood Cholesterol Increased	23	0.23	U
Breast Pain	23	0.23	U
Emotional Disturbance Nos	23	0.23	U
Inappropriate Adh Secretion	23	0.23	U
Migraine Nos	23	0.23	U
Muscle Spasms	23	0.23	U
Neck Pain	23	0.23	U
Petechiae	23	0.23	U
Heart Rate Increased	22	0.22	U
Multi-Organ Failure	22	0.22	U
Sleep Disorder Nos	22	0.22	U
Tongue Disorder Nos	22	0.22	U
Death	21	0.21	U
Caecal Abnormality Nos	21	0.21	U
Gastric Ulcer	21	0.21	U
Liver Fatty	21	0.21	U
Muscle Twitching	21	0.21	U
Oral Pain	21	0.21	U

PT	Count of PTs	Percent of Total	Labeled
Paranoia	21	0.21	U
Parosmia	21	0.21	U
Pulmonary Embolism	21	0.21	U
Respiratory Disorder Nos	21	0.21	U
Swelling Nos	21	0.21	U
Systemic Lupus Erythematosus	21	0.21	U
Blood Amylase Increased	20	0.20	U
Erythema Multiforme	20	0.20	U
Eye Disorder Nos	20	0.20	U
Fall	20	0.20	U
Hepatic Necrosis	20	0.20	U
Hypercholesterolaemia	20	0.20	U
Influenza Like Illness	20	0.20	U
Lung Disorder Nos	20	0.20	U
Lymphoma Nos	20	0.20	U
Speech Disorder Nec	20	0.20	U
Visual Disturbance Nos	20	0.20	U
Balance Impaired Nos	19	0.19	U
Blood In Stool	19	0.19	U
Bone Pain	19	0.19	U
Cardiovascular Disorder Nos	19	0.19	U
Hoarseness	19	0.19	U
Libido Decreased	19	0.19	U
Phlebitis Nos	19	0.19	U
Abdominal Pain Lower	18	0.18	U
Conjunctivitis Nec	18	0.18	U
Dyspepsia Aggravated	18	0.18	U
Mania	18	0.18	U
Oedema Upper Limb	18	0.18	U
Oesophageal Ulcer	18	0.18	U
Rash Generalised	18	0.18	U
Rhabdomyolysis	18	0.18	U
Skin Disorder Nos	18	0.18	U
Anuria	17	0.17	U
Congenital Abnormality Nos	17	0.17	U
Dysphonia	17	0.17	U
Haematocrit Decreased	17	0.17	U
Haemoptysis	17	0.17	U

PT	Count of PTs	Percent of Total	Labeled
Hepatomegaly	17	0.17	U
Idiopathic Thrombocytopenic Purpura	17	0.17	U
International Normalised Ratio Increased	17	0.17	U
Prostatic Disorder Nos	17	0.17	U
Rectal Bleeding	17	0.17	U
Taste Loss	17	0.17	U
Tongue Discolouration Nos	17	0.17	U
Unexpected Therapeutic Effect	17	0.17	U
Ventricular Extrasystoles	17	0.17	U
Visual Acuity Reduced	17	0.17	U
Bronchospasm Nos	16	0.16	U
Cholestasis	16	0.16	U
Colitis Nos	16	0.16	U
Diabetes Mellitus Nos	16	0.16	U
Disseminated Intravascular Coagulation	16	0.16	U
Drug Hypersensitivity	16	0.16	U
Intestinal Obstruction Nos	16	0.16	U
Nail Disorder Nos	16	0.16	U
Overdose Nos	16	0.16	U
Salivary Hypersecretion	16	0.16	U
Suicide Attempt	16	0.16	U
Appetite Increased	15	0.15	U
Blood Glucose Increased	15	0.15	U
C-Reactive Protein Increased	15	0.15	U
Coordination Abnormal Nos	15	0.15	U
Diplopia	15	0.15	U
Extrapyramidal Disorder Nec	15	0.15	U
Eye Pain	15	0.15	U
Faecal Incontinence	15	0.15	U
Gastroenteritis Helicobacter	15	0.15	U
Gastrointestinal Neoplasm Nos	15	0.15	U
Haematoma Nos	15	0.15	U
Hepatic Encephalopathy	15	0.15	U
Hyperlipidaemia Nos	15	0.15	U
Lethargy	15	0.15	U
Lipase Increased	15	0.15	U
Loose Stools	15	0.15	U
Mucous Membrane Disorder Nos	15	0.15	U

PT	Count of PTs	Percent of Total	Labeled
Nasopharyngitis	15	0.15	U
Prothrombin Time Prolonged	15	0.15	U
Rebound Effect	15	0.15	U
Splenomegaly	15	0.15	U
Thirst	15	0.15	U
Throat Tightness	15	0.15	U
Albuminuria Present	14	0.14	U
Candida Nos	14	0.14	U
Colitis Pseudomembranous	14	0.14	U
Electrocardiogram Abnormal Nos	14	0.14	U
Electrocardiogram Qt Prolonged	14	0.14	U
Feeling Hot	14	0.14	U
Hair Disorder Nos	14	0.14	U
Hypovitaminosis Nos	14	0.14	U
Movement Disorder Nos	14	0.14	U
Neurological Disorder Nos	14	0.14	U
Oral Discomfort	14	0.14	U
Papilloedema	14	0.14	U
Pelvic Pain Nos	14	0.14	U
Pulmonary Fibrosis	14	0.14	U
Pulmonary Oedema Nos	14	0.14	U
Sinusitis Nos	14	0.14	U
Vaginal Candidiasis	14	0.14	U
Ventricular Fibrillation	14	0.14	U
Ventricular Tachycardia	14	0.14	U
Vitamin B12 Deficiency	14	0.14	U
Ascites	13	0.13	U
Calculus Renal Nos	13	0.13	U
Coagulation Disorder Nos	13	0.13	U
Discomfort Nos	13	0.13	U
Disturbance In Attention Nec	13	0.13	U
Drug Level Nos Below Therapeutic	13	0.13	U
Feeling Cold	13	0.13	U
Frequent Bowel Movements	13	0.13	U
Joint Stiffness	13	0.13	U
Mental Impairment Nos	13	0.13	U
Mucosal Erosion Nos	13	0.13	U
Nightmare	13	0.13	U

PT	Count of PTs	Percent of Total	Labeled
Oesophageal Disorder Nos	13	0.13	U
Optic Atrophy	13	0.13	U
Polyuria	13	0.13	U
Rhinitis Nos	13	0.13	U
Torsade De Pointes	13	0.13	U
Urinary Incontinence	13	0.13	U
Visual Field Defect Nos	13	0.13	U
Accident Nos	12	0.12	U
Accidental Overdose (Therapeutic Agent)	12	0.12	U
Bacterial Infection Nos	12	0.12	U
Cataract Nec	12	0.12	U
Cerebral Ischaemia	12	0.12	U
Cholecystitis Nos	12	0.12	U
Collapse	12	0.12	U
Facial Palsy	12	0.12	U
Gingival Bleeding	12	0.12	U
Haemolysis Nos	12	0.12	U
Hiatus Hernia	12	0.12	U
Hypoglycaemia	12	0.12	U
Irritability	12	0.12	U
Joint Disorder Nos	12	0.12	U
Joint Swelling	12	0.12	U
Laryngospasm	12	0.12	U
Loss Of Consciousness Nec	12	0.12	U
Memory Impairment	12	0.12	U
Non-Accidental Overdose	12	0.12	U
Polyp Nos	12	0.12	U
Red Blood Cell Count Decreased	12	0.12	U
Restlessness	12	0.12	U
Thrombocythaemia	12	0.12	U
Vaginal Haemorrhage	12	0.12	U
Viral Infection Nos	12	0.12	U
Abnormal Behaviour Nos	11	0.11	U
Apathy	11	0.11	U
Breast Enlargement	11	0.11	U
Carcinoid Tumour Of The Stomach	11	0.11	U
Corneal Erosion	11	0.11	U
Cystitis Nos	11	0.11	U

PT	Count of PTs	Percent of Total	Labeled
Dementia Nos	11	0.11	U
Dialysis Nos	11	0.11	U
Difficulty In Walking	11	0.11	U
Dyskinesia Nec	11	0.11	U
Fungal Infection Nos	11	0.11	U
Gastric Ulcer Haemorrhage	11	0.11	U
Hair Colour Changes	11	0.11	U
Hyperkinetic Syndrome	11	0.11	U
Hyperplasia Nos	11	0.11	U
Hypocalcaemia	11	0.11	U
Hypoxia	11	0.11	U
Inflammation Nos	11	0.11	U
Metabolic Acidosis Nos	11	0.11	U
Micturition Urgency	11	0.11	U
Myoclonic Jerks	11	0.11	U
Myopathy	11	0.11	U
Oesophageal Pain	11	0.11	U
Oliguria	11	0.11	U
Osteoporosis Nos	11	0.11	U
Peripheral Vascular Disease Nos	11	0.11	U
Pharyngeal Disorder Nos	11	0.11	U
Skin Discolouration	11	0.11	U
Testicular Pain	11	0.11	U
Vaginitis	11	0.11	U
White Blood Cell Count Increased	11	0.11	U
Acne Nos	10	0.10	U
Atrioventricular Block Complete	10	0.10	U
Blood Iron Decreased	10	0.10	U
Blood Potassium Decreased	10	0.10	U
Cardiac Disorder Nos	10	0.10	U
Chest Pressure Sensation	10	0.10	U
Choking	10	0.10	U
Cyanosis Nos	10	0.10	U
Cyst Nos	10	0.10	U
Depersonalisation	10	0.10	U
Drug Withdrawal Syndrome	10	0.10	U
Earache	10	0.10	U
Epidermolysis Bullosa	10	0.10	U

PT	Count of PTs	Percent of Total	Labeled
Eyelid Oedema	10	0.10	U
Grand Mal Convulsion	10	0.10	U
Hepatic Neoplasm Malignant Nos	10	0.10	U
Hypercalcaemia	10	0.10	U
Irritable Bowel Syndrome	10	0.10	U
Pleural Effusion	10	0.10	U
Rash Papular	10	0.10	U
Red Blood Cell Abnormality Nos	10	0.10	U
Renal Colic	10	0.10	U
Respiratory Failure (Exc Neonatal)	10	0.10	U
Sexual Dysfunction Nos	10	0.10	U
Skin Odour Abnormal	10	0.10	U
Skin Ulcer Nos	10	0.10	U
Sputum Increased	10	0.10	U
Stupor	10	0.10	U
Transaminase Nos Increased	10	0.10	U

Attachment B

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 19 1992

FROM: Evelyn Farinas, RPh.
Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Joyce Johnson, D.O., M.A., Acting Director
Division of Epidemiology and Surveillance, HFD-730

10-19-92

TO: Stephen Fredd, M.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Monitored Adverse Reaction (MAR) Report:
Drug: Omeprazole (Prilosec®)
Reaction: Severe skin reactions:
Toxic Epidermal Necrolysis (TEN)
Stevens-Johnson Syndrome (SJS)
Erythema Multiforme (EM)

Introduction:

Prilosec® (omeprazole), manufactured by Merck, Sharp & Dohme, was first approved on September 14, 1989 as a 20 mg delayed release capsule. The name was changed in July, 1990 from Losec to Prilosec. Omeprazole is indicated for the short-term treatment of active duodenal ulcer, severe erosive esophagitis, poorly responsive gastroesophageal reflux disease (GERD), and for the long term treatment of pathological hypersecretory conditions (Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

Unlike other H2 antagonists which are reversible competitive blockers of histamine at the H2 receptors, omeprazole suppresses the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell, thus blocking the final step of gastric acid production. This effect is dose related and inhibits both basal and stimulated acid secretion irrespective of the stimulus. Onset of the antisecretory effect occurs within one hour, with the maximum effect occurring within two hours. However, the antisecretory effect of omeprazole lasts far longer due to its strong binding to the H+/K+ ATPase enzyme. When the drug is discontinued, the secretory activity returns gradually over 3 to 5 days.

Daily dosage varies according to the condition being treated. Doses of 20 mg daily for 4 to 8 weeks are recommended for the treatment of active duodenal ulcer and GERD. Adult doses for patients having hypersecretory conditions vary according to the individual needs. The recommended adult dose is 60 mg daily, but doses as high as 120 mg three times a day have been administered.

Adverse Reaction Labelling

"Rash" was reported as experienced by 1.5% of the patients on therapy during clinical trials with omeprazole. In addition, "skin inflammation, urticaria, pruritus, alopecia, dry skin, and hyperhidrosis" are mentioned under the Skin subsection of the Adverse Reactions section. Severe skin reactions such as TEN, SJS, and EM are not mentioned in the text.

Background Information on EM, SJS, and TEN

Erythema multiforme (EM) is an acute, self-limited eruption of the skin and mucous membranes characterized by distinctive target or iris lesions. EM refers to the cutaneous lesions alone, but the disease can be limited to or primarily affect mucosal surfaces. The etiology of EM is not clearly defined. Viral infections, drugs, neoplasms, deep x-ray therapy, contactants, endocrine agents, and collagen diseases have been implicated.

Stevens-Johnson syndrome (SJS) is associated with the involvement of several mucosal surfaces and internal organs, and accompanied by severe constitutional symptoms. SJS is characterized by a nonspecific prodrome of 1 to 14 days, and followed by appearance of inflammatory bullous lesions on the mucous membranes.

Toxic Epidermal Necrolysis (TEN) is the most serious cutaneous reactions to drugs. It is characterized by widespread erythema and detachment of epidermis resembling scalding. The onset is usually acute, although in many cases there are prodromal signs such as burning of the conjunctivae, skin tenderness, fever and malaise. As a general rule mucous membranes are involved (lips, oral mucosa, conjunctivae, as well as genital and anal mucous membranes). Outcome can be fatal. Survivors often develop sequelae, such as scarring of mucous membranes.

Selection of Cases:

We searched the FDA Spontaneous Reporting System under the mid-level code SKINGENSER to identify reports of any serious skin adverse reactions associated with omeprazole. The code includes the following COSTART terms:

DERM EXFOL	exfoliative dermatitis
EPIDERM NECRO	toxic epidermal necrolysis
ERYTHEMA MULT	erythema multiforme
NECRO SKIN	necrosis skin
STEVENS JOHNSON SYND	Stevens-Johnson Syndrome

Of the 10 unduplicated case reports identified, 4 cases reported erythema multiforme, 2 Stevens-Johnson syndrome, 1 toxic epidermal necrolysis, and 1 both erythema multiforme and toxic epidermal necrolysis. Two reports were not included because of lack of information and serious outcome. In addition, we identified 1 case (# 743770) which listed diphenhydramine as the suspect drug in the development of toxic epidermal necrolysis. Further review of this case indicates that omeprazole, but not diphenhydramine, should be the suspect drug. Therefore, a total of 9 cases of severe skin reactions associated with omeprazole will be presented. Copies of the case reports are attached for your information.

A literature search did not identify any case reports of severe skin reactions associated with omeprazole.

Demographics

sex:	female (5), male (3), unknown (1)
age:	mean 65.5 (range 39-82)
daily dosage:	20mg (4), 40 mg (3), unknown(2)
time to onset:	3 days (2), 10 days (1), 15 days (1), 17 days(1), 19 days (1), 30 days (2), 60 days(1)
dechallenge:	pos (4), neg (3), NA (1), unknown (1)
rechallenge:	pos (1), NA (3), unknown (5)
outcome:	hospitalization (4), death (2, of which 1 was unrelated to skin reactions), recovery after drug treatment (1), unknown (2)
location:	domestic (4), foreign (5)
report yr:	1992 (3), 1991 (3), 1990 (1), 1989 (1), unknown (1)
report type:	15-day (9)

Summary of Cases

The following table summarizes the cases presented.

Control # Type Year Location	Age Sex	Onset Daily Dose	Dech Rech Outcome	Reactions	Concom. Drugs
1.#825074 15-day 1992 AL	68 F	15 d 20 mg	Neg Unk Hosp	Physician reported case of a patient with a previous history of penicillin and sulfa allergies who, 15 days after initiation of treatment with omeprazole and metoclopramide, presented with swollen lips, blisters on lips and tongue, rash and red splotches over body. Symptoms persisted after medications were discontinued. Patient was hospitalized and received treatment with IV steroids and oral prednisone. Patient reported peeling on her hands, feet, and ears and loosening of her fingernails and toenails which were left attached only at the base. Dermatology consult and biopsy confirmed diagnosis of EM.	Metoclopramide
2.#842176 15-day 1992 UK	77 M	60 d? 40 mg	NA NA Hosp (Death not related to skin reactions)	Patient with a history of myocardial infarction developed erythema multiforme approximately 2 months after initiation of therapy. Death resulted from a myocardial infarction or pulmonary embolism, and was not drug related. Report states: "it was felt that the patient's erythema multiforme was possibly related to therapy with omeprazole".	Nifedipine Prednisolone Furosemide Ranitidine Isosorbide mononitrate

Control # Type Year Location	Age Sex	Onset Daily Dose	Dech Rech Outcome	Reactions	Concom. Drugs
3.#709789 15-day 1990 Sweden	74 F	2 d Unk	Pos Unk Hosp	Two days after initiation of therapy patient was hospitalized with fever and rash. Erythema multiforme was suspected. Patient's condition improved after treatment with steroids and acyclovir. Subsequently a diagnosis of possible Yersinia infection was made based on titers.	Unknown
4.#633641 15-day 1989 GA	41 F	3 d 20 mg	Pos Unk Tx. with drugs	Patient developed erythema multiforme 3 days after initiating treatment with omeprazole. She was treated with higher dosages of prednisone and recovered. Patient had been receiving Septra DS, Ketoconazole, and Prednisone for lymphoma 2 months prior to starting omeprazole.	Prednisone Septra DS Ketoconazole
5.#720676 15-day 1991 PA	39 M	30 d? 20 mg	Pos Pos Hosp	Patient developed Stevens-Johnson syndrome after second course of therapy with omeprazole. Patient was hospitalized, treated with prednisone, and recovered. He was given a third course of omeprazole, and developed a rash. Treatment was changed to ranitidine.	None
6.#747209 15-day Unk. Norway	Unk. Unk.	30 d 40 mg	Unk Unk Unk	Patient presented with Stevens-Johnson syndrome after 4 weeks of therapy with omeprazole. "The experience was felt to be life threatening."	Unknown
7.#747210 15-day 1991 Germany	71 F	17 d 40 mg	Neg Unk Perm disab	A patient with a history of hypertension received omeprazole therapy for 17 days, at which time she presented with toxic epidermal necrolysis. Condition was still present one week post discontinuation of omeprazole.	Ismelin Esidrix Ispaghula (herbal medicine used as a demulcent)

Control # Type Year Location	Age Sex	Onset Daily Dose	Dech Rech Outcome	Reactions	Concom. Drugs
8.#743770 15-day 1991 WA	73 M	7 d Unk	Neg NA Death	Ten days after discharge from the original hospitalization while taking omeprazole for treatment of gastrointestinal bleeding, the patient was readmitted with a rash and pneumonia. By the 6th day of hospitalization, the patient was markedly neutropenic, thrombocytopenic, and the rash had become blistering with sheets of epidermis being sloughed. A diagnosis of TEN was confirmed by biopsy. The patient's condition worsened requiring pigskin grafting. Over the next 24 hours the patient became hypothermic and his blood pressure could not be maintained even with the use of pressors. The patient died after coding twice.	Stool softener
9. 864628 15-day 1992 UK	82 F	19 d 20 mg	Pos NA Hosp	This 82 y.o. patient with liver cirrhosis, possible hepatitis and a history of mitral regurgitation and congestive heart failure was placed on omeprazole therapy to treat hematemesis. Concomitant medications included amphotericin, ciprofloxacin, spironolactone, ranitidine and terfenadine. Nineteen days into treatment the patient presented with a rash that "developed into questionable erythema multiforme and toxic epidermal necrolysis." The patient was then treated with IV cefotaxime, followed by oral antibiotics. Omeprazole was discontinued 8 days after symptoms appeared and the patient's condition had slightly improved 2 weeks later.	Amphotericin Ciprofloxacin Spirono-lactone Ranitidine Terfenadine

Discussion

In this report 9 cases of severe skin reactions associated with omeprazole are presented: EM (4), SJS (2), TEN (2), and EM with TEN (1).

There were 2 fatalities reported although 1 case appears not to be drug related. The patient in case 8 developed TEN and expired from bradycardia and hypotension 24 hours after undergoing skin grafting. The patient in case 2 developed EM, but the reporter felt that the death was from myocardial infarction or pulmonary embolism and probably not drug related.

In the 9 cases presented, a positive dechallenge is indicated in 4 cases (3, 4, 5 and 9) and a positive rechallenge is also indicated in case 5. In cases 1, 7, and 8 the symptoms did not abate once omeprazole was discontinued. This is consistent with EM, SJS, and with TEN where symptoms usually persist for 1 to 6 weeks.

Concomitant medications might have confounded the adverse events in some of these cases. In cases 2, 4, and 7 the patients were under therapy concomitantly with medications such as nifedipine, Septra, and Ismelin-Esidrix respectively, which may have confounded the skin reactions. However, in case 2 the patient had been on nifedipine therapy for several years (since approximately 1987) prior to omeprazole therapy, and in case 4 the patient had been receiving Septra for 2 months prior to omeprazole therapy. In case 7, although dates of therapy are provided for omeprazole and not for Ismelin-Esidrix which has been associated with SJS as stated in the labelling, this 71 year old patient was reported to have a history of hypertension which might indicate that the patient had been on treatment with this (Ismelin-Esidrix) or other antihypertensive for an extended time. Case 9 lists an array of medications (amphotericin, ranitidine, ciprofloxacin, spironolactone, and terfenadine) taken by this patient which also might have confounded the case.

However, case 5 listed omeprazole as sole therapy, and in cases 1 and 8, drug therapy consisted of omeprazole and only one other drug (metoclopramide and a stool softener respectively) which are not known to cause any severe skin reactions. In cases 3 and 6, which are foreign reports, it is unknown if the patients were using any concomitant medications, although none are listed.

All of the cases presented in this series suggest a strong temporal association between the severe skin events and omeprazole.

Conclusion

This report presents 9 cases of severe skin reactions (4 EM, 2 SJS, 2 TEN, 1 EM+TEN) temporally associated with omeprazole from the Spontaneous Reporting System. The cases presented here point to a greater degree of severity of skin related events than what is currently included in the labelling for this product.

[/S/]
Evelyn Farinas, RPh.

Concur:

APPEARS THIS WAY
ON ORIGINAL

[/S/]
Min Chen, RPh., M.S.
Acting Group Leader

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cc:
HFD-180/Gallo-Torres
HFD-700 Anello
HFD-730 Johnson
HFD-733 Freiman / Burke
HFD-735 Barash / Chen / MAR file / Bacsanyi
McCloskey / Farinas
NDA#

APPEARS THIS WAY
ON ORIGINAL

Attachment C

2+3

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 2 1994

FROM: Evelyn R. Farinas, R. Ph.
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Reports Evaluation Branch, HFD-735

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Acting Director
Division of Epidemiology and Surveillance, HFD-730

TO: Stephen Fredd, M.D., Director
Maria Walsh, CSO
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Consult: Visual disturbances associated with the use of Omeprazole (Prilosec).

This memo responds to Ms. Maria Walsh's Consult request for information on cases listing visual disturbances experienced in association with the use of omeprazole (Prilosec). This data is derived from the information reported to the FDA Spontaneous Reporting System (SRS) from 1992 until April 1994. We also looked at cases in the BGA package (Astra-Hassle's response to the Bundesgesundheitsamt [BGA] inquiry) which reported ophthalmic adverse events. Tables 1-5 provide a brief summary of the cases. A literature search was not successful in uncovering any articles associating visual disturbances with omeprazole.

Labeling information:

Under the Clinical Pharmacology section the labeling states that systemic effects of omeprazole in the CNS have not been found to date. However, under the Adverse Events section several CNS adverse events are mentioned such as headache, dizziness and vertigo. Visual disturbances are not mentioned in the label. Interestingly, several of the European labels include "blurring of vision" as an adverse event (personal communication, Dr. E. Leonard, Merck Regulatory Affairs, May 15, 1994). A copy of the UK data sheet is included.

SRS CASES

Selection of cases:

We searched the FDA SRS under the mid-level code OPH% to capture all cases of visual disturbances where omeprazole was listed as a suspect drug. This mid-level code includes 60 individual COSTART terms. A total of 40 unduplicated cases were identified of which 16 indicated a serious outcome (hospitalized 7, disability 6, both 3). See Tables 1 and 2 for a description of the cases. As of May 2 1994, the SRS contained 2079 reports listing any adverse event where omeprazole was listed as a suspect drug.

Demographics:

Sex: Male (19), Female (19), NS (2)
Age: 10 (1), 25-59 (21), 60-85 (13), NS (5)
Time to onset: <24^0 (5), 1-7 days (7), 1-2 weeks (3), 2-4 weeks (6), 1-2 months (1), 6-12 months (3), 13-18 months (2), NA (13)
Dosage form: PO (37), IV (2), PO + IV (1)
Source: Foreign (12), Domestic (28)
Year of report: 1989-90 (6), 1991-92 (10), 1993-94 (24)
Dechallenge: Positive (20), Negative (4), NA (16)
Rechallenge: Positive (4), Negative (1), NS (35)
Ophthalmic adverse events *:

Blurred vision		(11)
Vision loss		(5)
Papillary edema		(3)
Visual disturbances:	double vision	(2)
	poor vision	(1)
	dimmed vision	(1)
	photophobia	(1)
Visual disturbances NOS		(4)
Dry or burning eyes		(5)
Retinal detachment or deterioration		(2)
Hemorrhage sclera		(1)
Hemorrhage vitreous		(1)
Pain		(1)
Increased intraocular pressure		(1)
Cataracts		(1)

* Only the predominant ophthalmic adverse event for each case is listed.

Discussion:

1) IV administration

The 3 cases, originating in Germany, described serious adverse events in adult patients where the onset was under 1 month. All 3 cases were also described in the package.

- Vision loss (2)

The 2 cases in the SRS originated in Germany and reported optic nerve damage. Patients experienced amaurosis associated with optic nerve atrophy. The administration in both cases of multiple concomitant drugs and the severe trauma (burn patients) experienced by the patients confound these cases. The reports indicated one patient lost sight in the left eye permanently, and the other continued having periods of intermittent blindness alternating with tubular vision 3 months after discontinuation of omeprazole.

- Blurred vision (1)

In this German case, where the patient complained of blurred vision, papillary edema with thrombosis of the right nerve head was diagnosed subsequent to the administration of both IV and PO omeprazole. Although the symptoms started 1-2 days after the IV administration, vision did not improve when therapy was switched to oral omeprazole.

2) PO administration

Of the 37 cases, 9 were foreign and 28 were domestic; 13 indicated a serious outcome (disability 6, hospitalization 6, both 1); 16 demonstrated onset to be within 30 days of initiation of therapy; 22 described dosages of 20 mg daily; and 19 showed that patients recovered upon discontinuation of omeprazole.

- Vision loss (3)

Time to onset of blindness was short-term in 2 cases (after 1 day and 1 week of 20 mg/d therapy respectively) and long-term in the third (after 231 days of 10 mg/d therapy). The outcome for each case was a return to normal vision the following day in the first, unknown in the second and permanent vision loss in the third. In this third case, blindness was associated with vitreous humor degeneration.

- Blurred vision (10)

Onset of blurred vision in these 10 cases fluctuated from within 1 day to 8 months after initiation of therapy. All but 1 case indicated a positive dechallenge, and 3 also indicated a positive rechallenge. Only 3 reports, all foreign, indicated a serious outcome (hospitalization 2, disability 1) where 1 describes an overdose in which symptoms developed 20 hours after the ingestion of twenty 20-mg capsules. This reports further stated that the symptoms resolved within 32 hours. Of note is that in 2 cases additional adverse events (rash, hypotension, urticaria) might be indicative of an allergic reaction to omeprazole; in a third case visual disturbances were attributed to orthostatic dysregulation, and in a fourth case the patient had a long history of headaches and visual impairment.

- Vision disturbances (9)

Four cases described the adverse event only as a visual disturbance, and the remaining 5 categorized the adverse event as double vision, photophobia, diminished or poor vision. Adverse events were reported to occur from shortly after ingestion of only 1 dose to after 49 days of therapy. Five cases indicated positive dechallenge, and an additional case showed both positive dechallenge and rechallenge. Only 2 cases, each reporting visual disturbance, indicated a serious outcome (hospitalization 1, disability 1). In the only case where the patient was hospitalized, neurological examination confirmed a diagnosis of polyneuritis cranialis.

- Papillary edema (3)

All 3 foreign cases reported a serious outcome (hospitalization 1, disability 1, both 1) where patients received from 24 to 48 days of therapy before the onset of papilledema. No information was given on any case concerning dechallenge or rechallenge. Only 1 of the 3 cases indicated the patient had an ophthalmic examination preceding omeprazole therapy where "visual acuity from ———————————indicated right eye 1.0, left 1.0 with no papilledema."

- Dry eyes (4) and burning eyes (1)

Of these 5 cases, only 1 reported a serious outcome (hospitalization). In this case, the patient's non-ophthalmic adverse events (dry mouth, sore throat) which persisted after discontinuation of omeprazole were attributable to the patient's GERD. Of the remaining 4 cases, 2 indicated patients suffered diseases associated with dry eyes (familial dysautonomia and Sjoegren's respectively). In both cases the onset of increased severity of dry eyes developed after long term therapy with omeprazole (over 1 year in each case). A decrease in the dosing

of omeprazole from 30 to 20 mg daily improved the lacrimation in the dysautonomic patient. Decreasing the dosing frequency to 3 times a week also lessened the severity of symptoms (eyes burning) in the only case indicating a positive dechallenge.

- Visual disturbance associated with headache

Scant information was supplied in each of the 3 cases where headache was associated with a visual disturbance (increased intraocular pressure, photophobia and eye pain respectively), although all 3 indicated a positive dechallenge. In 2 cases patients also experienced nausea and vomiting. Of note is that in the case where the patient experienced eye pain, headache, nausea and vomiting, similar events had occurred on separate trials of therapy with omeprazole.

- Miscellaneous

Scant information is given in the remaining 5 cases. Two described the adverse event as retinal degeneration or detachment, 2 as hemorrhage of the sclera or vitreal, and 1 as cataracts. Information regarding the onset of adverse events was given only in the 2 hemorrhage cases, where it was described as under one week in both cases.

BGA package cases

On April 20, 1994 Merck & Co submitted as part of the BGA package a summary of 175 cases reporting ophthalmic adverse events which may contain duplicates. Both foreign and domestic cases were included. The line listings for these cases are attached as Tables 3, 4 and 5. Please note that 3 sets of databases were provided in the BGA package concerning omeprazole associated ophthalmic adverse events: Merck & Co.'s Worldwide Adverse Experience System [WAES], BGA's targeted cases and Astra's worldwide database. The possibility exists that any one case may appear in several of the databases.

Volume 1 of the BGA package contains statements by "expert ophthalmologists" who reviewed "the majority" of the cases referred to by the BGA. The 6 physicians who are associated with teaching institutions, 4 American and 2 German, reviewed all the cases involving serious events reported with IV administration. These "experts" concluded that a causal relationship between omeprazole and the reported ophthalmic events cannot be established.

A. Summary of cases in WAES database (as of March 8, 1994) reporting ophthalmic adverse events (Table 3):

Total number of cases:	52 (18 foreign, 34 domestic)
Dosage form:	PO (50), PO + IV (2)
Time to onset:	Range (1 day/1 dose to 518 days) ~ Average (135), Median (28)

Adverse events most often reported (4 or more)*:
Changes in visual acuity (20) [Blurred vision (11), Visual disturbance (4), Double vision (3), Visual changes (1), Xanthopsia (1)]
Retinal involvement (7) [Retinal detachment (2), Retinal hemorrhage (2), Retinal degeneration (1), Retinal occlusion (1), Retinal embolic disease (1)]
Cataract (4)

* May be more than 1 adverse event per report

1) IV administration

Omeprazole IV was concomitantly administered in 1 case, and possibly in a second. In these 2 cases, time to onset was 1-2 days. One patient suffered optic disc degeneration and optic nerve swelling. In both cases the patients complained of blurred vision.

2) PO administration

- Blurred vision: The time to diagnosis for the 9 cases ranged from 1 dose to 412 days. In the case indicating 412 days of therapy, the patient was further evaluated for hypoaldosteronism.

- Visual disturbance: Only 2 of the 4 cases indicated time to diagnosis, identified as 29 and 49 days respectively. In the second case, the unspecified visual disturbance subsided when metoclopramide was discontinued.

- Cataract: Long-term administration of omeprazole (range 112-363 days) characterizes 3 of the 4 cases reporting cataract. Two patients underwent surgery, and a third had the diagnosis confirmed by an ophthalmologist.

- Miscellaneous: Seven cases indicated an ophthalmic event associated with the retina: retinal detachment (2), retinal hemorrhage (2), occlusion retinal vessels (2) and retinal degeneration (1). Three indicated long-term therapy (119-462 days). In a fourth case, the patient suffered permanent vision loss in the left eye after 6 days of therapy. A diagnosis of central retinal vein occlusion was made. Past medical history was significant only in the retinal degeneration case, where the patient noticed its worsening after an unspecified length of therapy.

In attempting to match the cases listed in the WAES table with the SRS cases, it was noted that 12 of the 52 WAES cases were not identified in the FDA SRS. All 12 cases were foreign, and 8 indicated onset of adverse events after more than 100 days of therapy (range: 112-412 days). In the remaining 4, onset, dosage form and reported adverse events are as follows: 1) 2 days, PO or IV, blurred vision, 2) 15 days, PO, diplopia, 3) 12 days, PO, iritis, and 4) 4 days, PO, xanthopsia. The 12 cases have been highlighted in the attached WAES table.

B. Summary of targeted cases (as of March 8, 1994) reporting ophthalmic adverse events [adverse events from market experience in Germany] (Table 4):

Total number of cases:	22
Dosage form:	PO (16), IV (4), IV + PO (2)
Treatment duration:	Range (1-1095 days)
	Average (125 days), Median (8)
Most often reported:	Blurred vision (7)
	Visual impairment (4)
	Optic atrophy (3)
	Double vision (3)

1) IV and IV+PO administration

Of the 6 cases reporting IV dosing, 2 indicated patients had received 20 mg capsules also. Duration of therapy ranged from 1 to 44 days. All 6 patients were receiving 5 or more concomitant medications. The predominant ophthalmic adverse events reported were: optic atrophy (3), visual impairment (2) and blindness (1). In this last case, the patient received only IV omeprazole for 2 days. A fatal outcome is reported in 1 of the 2 cases reporting visual impairment, where a 33-year old female patient received IV dosing only.

2) PO administration

The most frequently reported adverse event was blurred vision (7). Three cases indicated vision loss which developed after short term therapy (less than 1 month). The reported adverse events associated with long-term oral therapy (>190 days) were blurred vision (1), visual impairment (1), diplopia (1) and retinal artery occlusion (1).

A copy of the summary table provided in Volume 1 of the BGA package is included (Table 3. Summary of the cases cited by the involving visual disturbances).

C. Summary of Astra's omeprazole market experience worldwide (up to March 17, 1994) reporting vision disorders:

Total number of cases:	101
Dosage form:	PO (95), IV (4), IV + PO (2)
Treatment duration:	
IV and IV+PO	Average (13 days), Range (1-44 days)
PO	Average (70.5 days), Range (1-1095 days)
Most often reported:	Blurred vision (25)
	Vision abnormality (16)
	Double vision (8)
	Vision disturbance (7)
	Vision impaired (7)
	Eye pain (7)

1) IV and IV+PO administration

These 6 cases correspond to the cases reported in the BGA targeted cases under the same subheading.

2) PO administration only

There was a total of 107 adverse events reported in the 95 cases, where blurred vision was the most frequently reported (25). Amaurosis fugax was reported in 4 cases, 3 of which indicated duration of therapy was over 210 days. In the one case reporting the longest duration of therapy (1095 days), retinal artery occlusion was also reported. In this case, the ophthalmologist stated that the occlusion could have been caused by an ischemic optical nerve atrophy. Copies of the cases were not available. A copy of the line listing provided in Volume 5 of the BGA package of all 101 cases is attached.

Summary

A brief summary of the cases in 4 available databases has been provided. These were the FDA SRS (40 cases), WAES (52 cases), the BGA targeted cases (22 cases) and Astra's worldwide market experience (101 cases). Information for the last 3 was obtained from the BGA package submitted by Merck & Co. Tables are attached providing brief description of the cases. Please note that a case may appear in 1 or more of the databases searched. Merck & Co. has indicated that work is in progress to correct for possible duplications and omissions.

In the SRS cases, which were individually reviewed, an assessment of causality is difficult due to the following factors: limited information provided in many of the cases, including lack of ophthalmic exam results; concomitant administration of multiple drugs in some cases; the presence of concomitant illnesses or conditions which confound some of the cases; and lack of a potential mechanism explaining this possible ocular toxicity. A temporal relationship is suggested by the event onset of 1 month or less in 21 cases, a positive dechallenge in 20 cases and positive rechallenge in 4 cases, although none of these cases stand out as "pivotal" examples of the possible reaction. If a relationship exists between omeprazole and these ocular events, the currently available information from the SRS cases suggests that the overall nature of such events is nonserious, of short-term onset and is reversible, although 3 of the patients reported permanent vision loss. Dr. Wiley Chambers, ophthalmologist in HFD-540, has been asked to review the SRS cases. His comments will be forwarded upon receipt.

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TABLE I - DOMESTIC CASES (ORAL ROUTE ONLY)

CASE # SRS # YR OF RT LOCATION	ADRs	AGE/ SEX MG/DAY OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
# 1 618826 89 UT	LOSS OF VISION DIZZINESS LIGHTHEADED	76/F 20 DISABLE	SAME DAY 1 DOSE ONLY	(+) NA	NONE	NS	EROSIVE ESOPHAGITIS VISION LOSS LASTED THROUGHOUT THE DAY. PATIENT RECOVERED THE NEXT DAY.
#2 744197 91 AZ	LOSS OF VISION LEFT EYE FLASHES VITREOUS HUMOR DEGENERATION LE	47/F 10 DISABLE	2?1 ON-GOING	NA NA	LEVOTHYROXINE	HEADACHES ABDOMINAL PAIN HX OF UTIs HYPOTHYROIDISM	DUODENAL ULCER OPHTHALMOLOGIST DIAGNOSED VITREOUS HUMOR DEGENERATION OF THE LEFT EYE. PATIENT LOST PART OF HER VISION WHICH IS NOT REVERSIBLE.
#3 1400304 93 PA	LOSS OF VISION	77/F 20 NS	7 DAYS NS	UNK UNK	NS	BILATERAL MACULAR DEGENERATION CENTRAL SCOTOMA COPD	GASTRIC ULCER SCANT INFORMATION PROVIDED.
#4 676514 90 CA	BLURRED VISION DRY MOUTH	60/M 20 TREATED WITH Rx DRUGS	10 DAYS 10 DAYS	(+) (+)	NS	NS	REFLUX ESOPHAGITIS PATIENT RECOVERED.
#5 726435 91 MO	BLURRED VISION PAIN AND BURNING IN THE CORNEA	51/F 20 NS	"SHORTLY AFTER" 29 DAYS	(+) (+)	FIORINAL KU-ZYME ACTIGALL LEVSIN	DRUG ALLERGIES	REFLUX ESOPHAGITIS PATIENT RECOVERED.
#6 763410 91 OH	BLURRED VISION DECREASED INTRA- OCULAR PRESSURE	62/M 20 NS	3½ WEEKS? 4 WEEKS	(+) NA	NONE	DRUG ALLERGIES RETINAL DETACHMENT RIGHT LENS IMPLANT FOR NUCLEAR CATARACT	REFLUX ESOPHAGITIS INTRAOCULAR PRESSURE DECREASED TO 4 IN RIGHT EYE. ONE WEEK FOLLOWING DISCONTINUATION OF OMEPRAZOLE PRESSURE INCREASED TO 16. THERE WAS NO EVIDENCE OF LEAK, IRITIS, OR RETINAL DETACHMENT.
#7 762187 91 SC	BLURRED VISION	85/F NS NS	NS NS	UNK UNK	NITROGLYCERIN CALAN TENORMIN CARAFATE	NS	NS SCANT INFORMATION PROVIDED.
#8 888195 92 PA	BLURRED VISION ("LEFT EYE OUT OF FOCUS")	59/M UNK NS	2 DAYS 2 DAYS	(+) UNK	CODEINE ASPIRIN	ARTHRITIS	PROPHYLAXIS OPHTHALMOLOGIC EXAM: VISION IN RIGHT EYE REMAINED 6/5 AND LEFT EYE DROPPED TO 6/9, WITH THE REMAINDER OF THE EXAM BEING NORMAL. PATIENT RECOVERED.

TABLE 1 - DOMESTIC CASES (ORAL ROUTE ONLY)

CASE # SRS # YR OF RT LOCATION	ADRs	AGE/ SEX MG/DAY OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
#9 1406327 93 NM	BLURRED VISION HEADACHE ERYTHEMATOUS MACULAR PAPULAR RASH PRURITUS	62/M 20 TREATED WITH Rx DRUGS	19 DAYS 19 DAYS	(+) NA	LISINOPRIL HYDROXIZINE CIMETIDINE VERAPAMIL SALSALATE ACETAMINOPHEN	PENICILLIN ALLERGY DIABETES MELLITUS HYPERTENSION DEGENERATIVE JOINT DISEASE	GERD PATIENT WAS TREATED WITH DIPHENHYDRAMINE AND RECOVERED 5 DAYS LATER.
#10 1422346 93 IA	BLURRED VISION URTICARIA DIZZINESS HYPOTENSION DIAPHORESIS PALLOR	73/M 20 TREATED WITH Rx DRUGS	SAME DAY 1 DOSE ONLY	(+) NA	HYTRIN NIACIN PRINIVIL	NS	EPIGASTRIC PAIN ADVERSE EVENTS OCCURRED WITHIN 2 HOURS OF OMEPRAZOLE DOSING.
#11 674987 90 CA	POOR VISION "PARKINSON'S SYMPTOMS"	73/F 20 TREATED WITH Rx DRUGS	34 DAYS ? 34 DAYS ?	(+) NA	REGLAN VISCOUS LIDOCAINE VENTOLIN ALUMIGEL	DRUG ALLERGIES	REFLUX ESOPHAGITIS NEUROLOGICAL EXAM CONFIRMED PARKINSONISM. VISION IMPROVED FIRST AFTER REGLAN WAS DISCONTINUED. PATIENT RECOVERED AFTER OMEPRAZOLE WAS ALSO DISCONTINUED.
#12 743448 91 OH	DIM VISION COUGH NUMBNESS IN CHEST AND ARMS	40 ?/M 20 NS	NS NS	(+) (+)	UNK	NS	UNKNOWN ON 3 SEPARATE OCCASIONS FOLLOWING THE INITIATION OF EACH DOSE, THE PATIENT EXPERIENCED BRIEF EPISODES OF COUGHING, NUMBNESS IN CHEST AND ARMS AND DIM VISION THAT LASTED 45 MINUTES TO AN HOUR .
#13 1421266 93 MI	DOUBLE VISION DRY EYES BURNING STOMACH ANXIETY	39/F UNK TREATED WITH Rx DRUGS	NS NS	(+) NA	XANAX	NS	ACID STOMACH THE PATIENT EXPERIENCED ADVERSE EVENTS WHILE TAPERING XANAX DOSING. DISCONTINUATION OF OMEPRAZOLE, INCREASED DOSING OF XANAX, AND ADDITION OF TOFRANIL TO THE REGIMEN RESULTED IN A PARTIAL RECOVERY.
#14 912450 92 KS	CHANGES IN VISUAL ACUITY	59/M 20 NS	36 DAYS ON-GOING	NA NA	IPRATROPIUM AMITRIPTYLINE POTASSIUM CHLORIDE CAPTOPRIL RANITIDINE	NS	DUODENAL ULCER SCANT INFORMATION PROVIDED.
#15 1408342 93 PA	VISUAL DISTURBANCES	77/F 20 NS	NS ON-GOING	NA NA	NS	MACULAR DEGENERATION HYPERTENSION	GASTRIC ULCER VISUAL DISTURBANCES SUBSIDED DESPITE CONTINUING THERAPY WITH OMEPRAZOLE. NO CLARIFICATION WAS GIVEN REGARDING THE NATURE OF THE VISUAL DISTURBANCES.

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CASE # SRS # YR OF RT LOCATION	ADRs	AGE/ SEX MG/DAY OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
#16 741455 91 MI	EYES BURNING	71/F 20 NS	7 DAYS ON-GOING	(+) NA	REGLAN ZANTAC	DRY EYES	PEPTIC ESOPHAGITIS REDUCTION OF DOSING TO 20 MG 3 TIMES A WEEK DECREASED THE "BURNING."
#17 762223 91 MI	EYES DRY MOUTH DRY ANXIETY DRY AND SORE THROAT DRY AND SORE TONGUE	54/F NS HOSP.	NS NS	(-) NA	REGLAN ANTACIDS	NS	GERD ALL ADRs EXCEPT DRY EYES PERSISTED DESPITE DISCONTINUATION OF OMEPRAZOLE. PHYSICIAN FELT THAT REPORTED DRY THROAT AND TONGUE WERE SYMPTOMS OF PATIENT'S GERD.
#18 1400367 93 MD	EYES DRY	NS NS NS	NS NS	NS NS	NS	NS	NS SCANT INFORMATION PROVIDED
#19 1400415 93 AZ	EYES DRY	55/F 20 NS	17 MONTHS NS	(-) NA	NS	ULCER SJOEGREN'S SYNDROME	HIATAL HERNIA PATIENT'S DRY EYES PERSISTED AFTER DISCONTINUATION OF OMEPRAZOLE. REPORTING PHYSICIAN FELT THAT THE EXPERIENCE WAS NOT RELATED TO OMEPRAZOLE THERAPY.
#20 1400591 93 PA	EYES DRY DECREASE IN LACRIMATION	18/M 30 NS	14 MONTHS ON-GOING	NA NA	REGLAN FLORINEF SENOKOT	FAMILIAL DYSAUTONOMIA	GASTRIC HYPERSECRETION PATIENT'S FURTHER DECREASE IN LACRIMATION IMPROVED UPON REDUCTION IN DOSAGE FROM 30 MG TO 20 MG PER DAY.
#21 692593 90 SD	DETERIORATION OF RETINAL DEGENERATION	54/M 20 HOSP.	NS NS	UNK UNK	NS	RETINAL DEGENERATION	GERD SCANT INFORMATION PROVIDED.
#22 1400418 92 OH	RETINAL DETACHMENT	UNK/F NS NS	NS NS	UNK UNK	NS	NS	NOT STATED SCANT INFORMATION PROVIDED. THE REPORTING PHYSICIAN FELT THAT OMEPRAZOLE WAS NOT THE CAUSE OF THE DETACHED RETINA. THERAPY WITH OMEPRAZOLE WAS DISCONTINUED.
#23 644521 0 NC	HEM SCLERA PRESSURE INSOMNIA	54/M NS NS	3 DAYS 8 WEEKS	(+) NA	NONE	NS	NOT STATED SUBCONJUNCTIVAL HEMORRHAGE IN THE RIGHT EYE RESOLVED SPONTANEOUSLY. INSOMNIA RESOLVED 5 DAYS AFTER DISCONTINUATION OF OMEPRAZOLE.

TABLE I - DOMESTIC CASES (ORAL ROUTE ONLY)

CASE # BRS # YR OF RT LOCATION	ADRs	AGE/ SEX MG/DAY OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
#24 1416431 93 NY	HEM VITREOUS	49/M 20 DISABLED	5 DAYS 7 DAYS	UNK UNK	CARAFATE	ALLERGY TO COSMETICS, POLLEN AND DRUGS	ACUTE ESOPHAGITIS AND GASTRITIS SLIT LAMP EXAMINATION INDICATED VITREOUS HEMORRHAGE.
#25 726569 90 PA	HEADACHE INCREASED INTRA-OCULAR PRESSURE	UNK/M 20 NS	NS NS	(+) NA	NONE	HISTORY OF HEADACHES AND INCREASED INTRA-OCULAR PRESSURE	REFLUX ESOPHAGITIS SCANT INFORMATION PROVIDED
#26 1408374 93 NY	HEADACHE EYE PAIN RE NUMBNESS RE NAUSEA VOMITING	UNK/F NS NS	NS NS	(+) (+)	NS	NS	NS PATIENT EXPERIENCED SIMILAR SYMPTOMS ON 2 SEPARATE ADMINISTRATIONS OF OMEPRAZOLE. ON BOTH OCCASIONS SYMPTOMS RESOLVED IN A FEW DAYS.
#27 1406404 93 OK	HEADACHE PHOTOPHOBIA NAUSEA VOMITING	46/F NS NS	NS NS	(+) NA	NS	MIGRAINES HYSTERECTOMY	NS CT SCAN OF HEAD WAS NORMAL. HEADACHE RESOLVED GRADUALLY A FEW DAYS AFTER DISCONTINUATION OF OMEPRAZOLE.
#28 1408528 93 OH	CATARACTS	NS/NS NS NS	NS NS	NS NS	NS	NS	NS A PATIENT DEVELOPED CATARACTS WHILE ON OMEPRAZOLE THERAPY. NO ADDITIONAL INFORMATION PROVIDED.

Table 2 - FOREIGN CASES IN THE SRS

CASE # SRS # YR OF RT LOCATION	ADRs	AGE/ SEX MG/DAY ROUTE OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
#1 1347071 93 GERMANY	AMAUROSIS OPTIC NERVE ATROPHY LE	28/M 80 X 1 DAY, THEN 40 IV HOSP. DISAB.	5 DAYS 18 DAYS	(-) NA	PRIMAXIN FLUCONAZOLE CEFTAZINE GENTAMYCIN CIPROFLOXACIN SULBACTAM PIRENZEPINE RANITIDINE AMBROXOL ACETYLCYSTEINE DOPAMINE KETAMINE FLUNITRAZEPAM	SEVERE BURN INJURY ALCOHOLISM INHALATION INJURY/BRONCHOPNEUM	NS FIXED DILATED PUPIL OF THE LEFT EYE WAS DISCOVERED ONE DAY AFTER STARTING THERAPY WITH 6000 MG OF PRIMAXIN PATIENT ON RESPIRATOR FOR OVER 5 WEEKS IMMEDIATELY PRIOR TO OMEP. THERAPY
#2 1376143 93 GERMANY	VISION LOSS OPTIC ATROPHY LE AND RE AMAUROSIS LE	28/M 40-120 IV HOSP. DISAB.	27 DAYS 34 DAYS	NA NA	PRIMAXIN PIRITRAMIDE KETAMINE MIDAZOLAM PORPOFOL FLUNITRAZEPAM PHENOBARBITAL DEHYDROBENZPERIDOL AMBROXOL N-ACETYL CYSTEINE DOPAMINE METAMIZOL GENTAMICIN CIPROFLOXACIN CEFTAZIDIME FLUCONAZOLE HEPARIN SODIUM	SEVERE BURNS ALCOHOLISM INHALATION TRAUMA	ULCER PROPHYLAXIS INTERMITTENTLY THROUGHOUT THE PERIOD OF OMEPRAZOLE THERAPY THIS PATIENT WAS ON A RESPIRATOR, RECEIVED HIGH DOSES OF PHENOBARBITAL AND PRIMAXIN, AND OTHER MULTIPLE DRUG THERAPIES. LOSS OF VISION EVIDENT 3 DAYS AFTER DISCONTINUATION OF OMEPRAZOLE. THE REPORTING PHYSICIAN INDICATED THAT THE PATIENT'S OPTIC NERVE ATROPHY MAY HAVE RESULTED FROM HIGH DOSES OF PHENOBARBITAL AND OR PRIMAXIN, OR FROM DRUG INTERACTIONS. PATIENT IS RECOVERING SOME TUBULAR VISION.
#3 978874 93 GERMANY	BILATERAL PAPILLARY EDEMA PALE FUNDUS BLURRED VISION	56/M 20 IV X 4 DAYS, THEN PO X 3 DAYS HOSP.	1-2 DAYS 7 DAYS	(-) NA	SOSTRIL (RANITIDINE) STILAMIN (SOMATOSTATIN) HEPARIN	BILLROTH II SURGERY ANEMIA ANASTOMOTIC ULCER	GI BLEEDING PATIENT DEVELOPED BLURRED VISION ON DAY OF OR DAY AFTER INITIATION OF IV OMEPRAZOLE THERAPY. SYMPTOMS PERSISTED AFTER SWITCHING TO ORAL THERAPY 3-4 DAYS LATER. OPHTHALMOLOGIC EXAM INDICATED BILATERAL PAPILLARY EDEMA WITH VENOUS CONGESTION AND MARKEDLY PALE FUNDUS. THROMBOSIS OF THE RIGHT NERVE HEAD WAS DIAGNOSED.

Table 2 - FOREIGN CASES IN THE SRS

CASE # SRS # YR OF RT LOCATION	ADR:	AGE/ SEX MG/DAY ROUTE OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
#4 93776 93 SWEDEN	BILATERAL PAPILLEDEMA HEADACHE VISUAL IMPAIRMENT	70/M 20 PO HOSP. DISAB.	4 WEEKS 4 WEEKS?	NA NA	UNK.	NS	HIATAL HERNIA THIS PATIENT DEVELOPED INTRACRANIAL HYPERTENSION AND BILATERAL PAPILLEDEMA. ON FOLLOW-UP THE PHYSICIAN REPORTED THAT A CAUSE FOR THE INTRACRANIAL HYPERTENSION HAD BEEN FOUND WHICH WAS NOT RELATED TO OMEPRAZOLE THERAPY. THE CAUSE WAS NOT IDENTIFIED IN THE REPORT.
#5 E1431204 94 GERMANY	EDEMATOUS LEFT PAPILLA LEFT OSCILLOPSIA PAIN ON MOVING	48/M UNK. PO DISAB.	5½ MONTHS ? UNK.	UNK. UNK.	TRAMAL VALORON NOVAMINSULFON ANESTHETIC	CERVICAL SPINE AND CHRONIC LUMBAR SPINE PAIN SYNDROME	UNKNOWN PATIENT COMPLAINED OF VISUAL SYMPTOMS ABOUT 5½ MONTHS AFTER INITIATION OF OMEPRAZOLE. VISUAL ACUITY TESTS UP TO THE INITIATION OF THIS THERAPY INDICATED RE AND LE 1.0 WITH NO PAPILLEDEMA.
#6 N1437510 94 GERMANY	LATERAL PAPILLEDEMA RE LOSS OF VISUAL ACUITY RE	75/M 20 PO HOSP.	24 DAYS 43 DAYS	UNK UNK	SALBUTAMOL AUGMENTIN DEPOT II INSULIN	COPD INFECTION DM VENTRICULAR ULCER DUODENAL ULCER BASAL CELL CA HYPERTHYROIDISM ALCOHOLISM	REFLUX ESOPHAGITIS PATIENT DEVELOPED EXTENSIVE LOSS OF RIGHT VISUAL ACUITY AND LATERAL PAPILLEDEMA, INTERPRETED BY THE OPHTHALMOLOGIST AS ISCHEMIC.
#7 1401858 93 GERMANY	BLURRED VISION TACHYCARDIA DYSPNEA SUPRAVENTRICULAR EXTRASYSTOLE	25/F 20 PO HOSP.	UNK UNK	(+) (+)	ETHYNIL-ESTRADIOL	ENDOMETRIOSIS PRE-EXCITATION SYNDROME	GASTRITIS RECHALLENGE WITH OMEPRAZOLE LED TO DYSPNEA AND TACHYCARDIA, BUT NOT VISUAL DISTURBANCES. VISUAL IMPAIRMENT WAS ATTRIBUTED TO ORTHOSTATIC DYSREGULATION.
#8 1422591 93 GERMANY	DOUBLE VISION INCOMPLETE PERIPHERAL LEFT FACIAL NERVE PARESIS	24/F 20 PO HOSP.	14 DAYS 14 DAYS	(+) UNK	CONTRACEPTIVE	TOXOPLASMOSIS	GASTRITIS NEUROLOGIC EXAM 1 WEEK AFTER DISCONTINUATION OF OMEPRAZOLE INDICATED POLYNEURITIS CRANIALIS (PARAINFECTIOUS) AND FIRST MANIFESTATION OF MS. PATIENT RECOVERED.

Table 2 - FOREIGN CASES IN THE SRS

CASE # SRS # YR OF RT LOCATION	ADR	AGE/ SEX MG/DAY ROUTE OUTCOME	ONSET DURATION OF THERAPY	DECH RECH	CONCOM. DRUGS	CONCOM. DISEASE	INDICATION COMMENTS
#9 E1431874 94 UK	BLURRED VISION OVERDOSE DROWSINESS DRY MOUTH HEADACHE	46/M 20 X 20 MG PO HOSP	20 HOURS UNK	(+) UNK	UNK	UNK	UNK PATIENT RECOVERED. SYMPTOMS RESOLVED WITHIN 32 HOURS.
#10 G1430398 94 GERMANY	BLURRED VISION DECREASED VISUAL ACUITY HEADACHE DIZZINESS	46/F 20 -40 PO DISAB.	8 MONTHS 12 MONTHS	(+) NA	PHENAZON (MIGRAN-KRANTIT) TRANSANNON (DHE AND CONJUGATED ESTROGENS)	HEPATITIS SMOKER GI HEMORRHAGE HYSTERECTOMY HYPOTENSION ESR INCREASED BREAST CANCER	DUODENAL ULCER PATIENT HAD TAKEN OMEPRAZOLE IRREGULARLY PRIOR TO ONSET OF SYMPTOMS. IN THIS PATIENT THE VISUAL IMPAIRMENT AND HEADACHES EXISTED FOR DECADES, AND INTENSIFIED AFTER OMEPRAZOLE THERAPY.
#11 936716 93 GERMANY	VISUAL DISTURBANCES HYPERTENSIVE CRISIS DIZZINESS HEADACHE NAUSEA AND VOMITING	51/F 20 X 1 DOSE PO DISAB.	1 DOSE 1 DOSE	(+) NA	TALINOLOL	HYPERTENSION	GASTRIC ULCER SYMPTOMS DEVELOPED AFTER 1 ORAL DOSE. PATIENT RECOVERED.
#12 N1437491 94 GERMANY	VISUAL DISTURBANCES HEADACHES DEPRESSION NIGHTMARES MUCOSAL EXSICCOSIS	51/F 20 PO NS	NS 3 DAYS	UNK UNK	NS	POLYARTHRITIS	GASTRITIS PATIENT RECOVERED SUBSEQUENT TO DISCONTINUATION OF OMEPRAZOLE THERAPY.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

(# 13)

TO (Division/Office) HFD-733			FROM: HFD-180	
DATE April 26, 1994	IND NO.	NDA NO. 19-810	TYPE OF DOCUMENT	DATE OF DOCUMENT 4/20/94
NAME OF DRUG Prilosec Delayed-Release Caps. (omeprazole)		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE 6/20/94

NAME OF FIRM Astra/Merck Group of Merck & Co., Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☒ ADVERSE REACTION REPORT
- ☐ MANUFACTURINGCHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS-
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☒ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: The sponsor has submitted the package prepared for the of Germany inquiry into serious visual and auditory adverse events reported in patients receiving the intravenous dosage formaulation of omeprazole. Please review this package as part of our April 5, 1994 request for you to investigate reports of visual disturbances with the use of omeparzole (oral and IV) both domestic and foreign.

J.D.

ENTERED 5-5-94

cc:HFD-180/M.Walsh

SIGNATURE OF REQUESTER	METHOD OF DELIVERY *(Check one)*
[illegible]	☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER
[illegible]	[illegible]

APPEARS THIS WAY ON ORIGINAL

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Attachment D

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 12, 1995

FROM: Carol Pamer, R.Ph., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Acting Division Director
Division of Epidemiology and Surveillance, HFD-730

TO: Stephen Fredd, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Consult: Visual disturbances associated with the use of omeprazole (Prilosec®)
Update to original consult of 8/22/94

Background

A consult request was received from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) to provide an update to an original consult regarding visual disturbances associated with the use of omeprazole (Prilosec®). A copy of this consult is included for reference purposes (see Attachment #1).

Omeprazole (Prilosec®) was approved for use in the U.S. on September 14, 1989 as a 20mg oral delayed release capsule. An intravenous formulation of omeprazole is also available for use in several other countries. Omeprazole has been characterized as a gastric acid-pump inhibitor, in that it suppresses gastric acid secretion by inhibiting the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell and blocks the final step of acid production. Prilosec® capsules are approved in the U.S. for short term therapy of active duodenal ulcer, erosive esophagitis, and symptomatic gastroesophageal reflux disease poorly responsive to customary medical therapy. The recommended adult daily dose for these conditions is 20mg. The oral capsules are also indicated for long term therapy of pathological hypersecretory conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis. The recommended adult starting dose for these conditions is 60mg, with doses of up to 120mg t.i.d. having been used.

Current Labeling

As of the June 1995 revision of the product labeling for Prilosec® delayed-release capsules (Astra Merck, U.S.), no ophthalmologic events or visual disturbances are labeled.

Selection of Cases

Currently (as of 10/95), there are 2915 total adverse events of any nature in the FDA

Spontaneous Reporting System (SRS) database for omeprazole.

The SRS was searched using the midlevel term OPH%, which encompasses 65 individual COSTART terms of ophthalmologic events. This results of this search as of 7/10/95 showed that there were 76 reports with one of these ophthalmologic COSTART terms where omeprazole was listed as the suspect drug. The counts of the most frequently occurring COSTARTs with 2 or more reports are as follows: VISION ABNORM 22, AMBLYOPIA 10, BLIND 10, ATROPHY OPTIC 7, CATARACT 7, EYE DIS 6, PAPILLEDEMA 6, DRY EYE 5, PAIN EYE 5, VISUAL FIELD DEFECT 5, DIPLOPIA 4, NEURITIS OPTIC 4, HEM EYE 3, RETINAL DETACH 3, VITREOUS DIS 3, CONJUNCTIVITIS 2, HEM RETINAL 2, and OCCLUS RETINAL ART 2. There is overlap in these numbers due to the fact that duplicate reports may exist and each report may contain up to 4 COSTART terms.

All reports were retrieved which had been received by the FDA during the period following the previous search (e.g., 5/2/94 to 7/10/95). This search yielded a total of 31 unduplicated cases which were individually reviewed. Table 1 summarizes various characteristics of these cases.

Table 1: CHARACTERISTICS of OPHTHALMOLOGIC events reported to SRS*

SEX	Male 20; Female 11
AGE (n=29)	Mean, 55 y.o. Median, 57 y.o. Range, 19-96 y.o. 0-19: 1 50-59: 7 20-29: 3 60-69: 9 30-39: 3 70-79: 2 40-49: 2 ≥80: 2
ROUTE OF ADMINISTRATION	Oral 25; IV 1; Both Oral and IV 4; Unknown 1
DAILY DOSAGE**	ORAL (n=27) Mean, 33 mg Median, 20 mg Range 20 mg, 15 40 mg, 9 80 mg, 3 INTRAVENOUS (n=5) Mean, 96 mg Median, 80 mg Range, 80 mg, 4 160 mg, 1
TIME TO ONSET (DAYS)† (n=23)	Mean, 186 days Median, 21 days Range, 1-1371 days 1-7 days, 8 8-14 days, 1 15-30 days, 4 31-90 days, 2 91-120 days, 3 121-250 days, 2 >900 days, 3
OPHTHALMOLOGIC ADVERSE EVENTS‡	ATROPHY OPTIC 5 NEURITIS OPTIC 4 EYE DIS 3 CATARACT 2 HEM EYE 2 PAPILLEDEMA 1 ARTERITIS 1 HEM RETINAL 1 RETINAL DETACH 1 RETINITIS 1 UVEITIS 1 Other visual disturbances (9): BLIND 3 DIPLOPIA 2 AMBLYOPIA 1 VISION ABNORM 1 MYDRIASIS 1 VISUAL FIELD DEFECT 1
DECHALLENGE	Positive 4; Negative 12; N/A or Unknown 15
RECHALLENGE	N/A or Unknown 31
TYPE OF REPORT	15-Day 23; Periodic 6; Direct 2
OUTCOME	Hospitalization 5; Disabled§ 11; Both 5
LOCATION	Domestic 10; Foreign 21

*Unless otherwise indicated, n=31. Time period covers 5/2/94 to 7/10/95.
**Highest dose received prior to or at the time of first reported ophthalmologic events.
†Sequential use, regardless of dosage form administered.
‡Only the predominant ophthalmologic adverse event for each case is listed.
§Defined as cases where permanent or unrelenting visual changes were reported.

Summary of cases

Individual ophthalmologic events were grouped according to the predominant diagnosis and summarized as follows. Sanitized copies of cases have been included for your information (see Attachment #2).

ATROPHY OPTIC--Five (5) cases were received which reported optic atrophy as the primary event observed. All of the cases were German reports. All reported persistent or permanent changes in vision at the time of the report and/or follow-up. All 5 patients had received oral omeprazole therapy. Two (2) patients also had received intravenous therapy

Case 1, a 57 y.o. male, had preexisting progressing fundus hypertonicus with beginning optic atrophy, as well as other medical problems and opthalmologic disorders prior to the use of omeprazole (oral 20mg/day, time to onset=167 days).

Case 2 was reported in a 28 y.o. female on both oral and intravenous therapy. Day 19 she experienced a sudden onset of nystagmus, visual impairment, oscillopsia, and abducens paresis. Ophthalmologic consult on Day 21 indicated anterior ischemic optic neuropathy. She was later diagnosed with acute neuromyelitis optica.

Case 3 was a 58 y.o. male with iron deficiency, anemia, osteomalacia, benign prostatic hypertrophy, irritable bladder and abuse of analgesics (aspirin, paracetamol) and tranquilizers (bromazepam). He experienced left central retinal artery occlusion after 2 to 3 years of therapy with omeprazole 40mg/day orally. Concomitant medications were unknown. The ophthalmologist also felt that the condition could be caused by ischemic optic nerve atrophy.

Case 4 occurred in a 71 y.o. male who was treated with oral and intravenous omeprazole for severe ulcerous esophagitis which developed during the postoperative period after amputation of both feet. His preexisting medical conditions included occlusive arterial disease, sepsis, dehydration, terminal renal insufficiency, sarcoidosis, anemia, hyperparathyroidism, candida mycosis, clostridia enteritis, and history of myocardial infarction. He was also on several other medications. The onset of ophthalmologic symptoms was reported as Day 21 of therapy, with loss of vision reported in the left eye. Ophthalmologic exam on Day 22 suspected occlusion of A.ophthalmica, though no abnormalities were detected. A second ophthalmologic exam Day 23 indicated that spontaneous recanalization was suspected. Day 24 an MRI indicated cerebral lesions with some "disturbed cerebral circulation" and a smaller older left cerebral infarction was detected. Omeprazole was discontinued on Day 27 of therapy. Left optic nerve atrophy "most likely of vascular origin" was diagnosed 8 days after omeprazole was discontinued and loss of vision persisted.

Case 5, optic atrophy and permanent visual impairment, occurred in a 56 y.o. male after approximately 960 days of omeprazole 20mg/day p.o. He experienced visual impairment, omeprazole was withdrawn approximately 49 days later, with no change in visual acuity. Cardiovascular origin was excluded.

NEURITIS OPTIC (4)--There were 4 cases of optic neuritis, all of which were foreign (3 Germany, 1 Sweden).

Case 1, a 28 y.o. female with preexisting severe myopia with partial loss of vitreous body and degenerative retinal changes, experienced worsening of preexisting conditions and optic neuritis after approximately 110 days of omeprazole, was later diagnosed with systemic lupus erythematosus.

Case 2, a 49 y.o. male on omeprazole 80mg/day i.v. for 1 day, 160mg i.v. on Days 2-4, and cisapride. He also had a history of nicotine and alcohol abuse. On Day 2, he experienced blurred vision and impaired left visual field. Therapy was switched to 80mg/day p.o. Days 5-8, then subsequently decreased to 20mg/day p.o. on Days 9-25. Visual symptoms persisted. Therapy with omeprazole was discontinued and an ophthalmologist was consulted 8 days later. Exam revealed central visual acuity of both eyes oc 1.0 at mild myopia. No active disease was seen, no pathological retinal findings and no changes of the papilla were found, although narrowed temporal visual field of left eye was noted. CT scan revealed no relevant pathological findings. Approximately 2 months later, symmetric temporal scotomas of the right eye were noted. Patient was diagnosed with suspected intracerebral ischemia in the area of the visual pathway without exact localization. Papilla of the left eye was found to be somewhat paler and some pigment accentuation was present. Differential diagnosis of "ischemic optic neuropathy or toxic lesion of the optic nerve due to therapy with omeprazole" was considered. Vision had

not improved at the time of the report.
Case 3, a 42 y.o. male, was on omeprazole 40mg/day p.o. for 5 days, 80mg/day i.v. for 4 days during a hospitalization for collapse and severe anemia, then oral omeprazole was restarted. Shortly after he was discharged, he complained of increasing visual impairment (~Day 41). CT scan was normal. He was later diagnosed with suspected vascular ischemic optic neuropathy, which was thought to be related to his smoking. Visual impairment gradually receded though he required corrective lenses (not previously required).
Case 4, a 55 y.o. female on omeprazole 40mg/day p.o. for 8 days, experienced blurred vision of the right eye on Day 3, which spontaneously cleared after some days. Dosage was decreased to 20mg/day p.o. on Days 9-48 (estimate). Day 48 of omeprazole, blurred vision reappeared and persisted. Omeprazole was discontinued. An ophthalmologic exam 15 days later diagnosed a right edematous papillitis/neuritis, narrow fundic vessels, which was interpreted as "subischemia without clinical correlae". Visual impairment and visual reduction remained unchanged. Later right optic nerve atrophy was diagnosed and judged as a terminal stage of ischemic optic neuropathy. There was no evidence of inflammatory disease present. Both positive dechallenge and rechallenge were indicated though it was not clear from the narrative of events to what points in time and omeprazole dosing this referred.

EYE DIS (3)--Three cases were received that were COSTARTed as EYE DIS, all of which were domestic cases. Two (2) were reports of discoloration of contact lenses during omeprazole oral use, one of which reported a positive dechallenge. Concomitant medications included albuterol and terfenadine in one patient and beclomethasone nasal spray, cisapride, ranitidine, dicyclomine, and azatidine/pseudoephedrine in the second patient.
Case 3 was from an ophthalmologist regarding a patient who experienced a change in the shape of her eye and lens during use of omeprazole 20mg/day p.o., with a positive dechallenge occurring after omeprazole was discontinued. It was unknown if she was on other medications. "No relevant medical history" was reported.

CATARACT (2)--A 64 y.o. male study participant in the U.K. on omeprazole 40mg/day p.o. for 1078 days experienced reduced vision due to cataract in his right eye. Cataract was removed, study drug continued unchanged.
A male patient (U.S.) in his 30's experienced visual problems after approximately 152 days of therapy with omeprazole 20mg/day p.o. He was diagnosed with cataracts. It was stated that he was on no other medications during that time period and had no other relevant health problems.

HEM EYE (2)/HEM RETINAL (1)--One domestic case of eye hemorrhage secondary to hypertension was received from a consumer (68 y.o. female) who was taking omeprazole 20mg/day orally for approximately 111 days prior. A 96 y.o. female (Germany) experienced conjunctival hemorrhages and thrombocytopenia, as well as other hemorrhagic events after 6 days of omeprazole therapy; the case was confounded by the use of fluoxetine. She expired 4 days after omeprazole was discontinued, with probable cause of death indicated as malnutrition, thrombocytopenia, and renal insufficiency. A pharmacist (U.S.) reported that 55 y.o. female developed a "hemorrhage in her lower eye" after an unspecified duration of therapy with omeprazole 20mg/day p.o. Other medications included Trinsicon®, zolpidem, chlorzoxazone, atenolol, and phenytoin. She was reported to recover with the experience not attributed to omeprazole.

PAPILLEDEMA--One (1) case was received from Germany, a 55 y.o. male with preexisting papilledema of the right eye, who was on omeprazole 40mg/day for 14 days and experienced papilledema and impaired visual acuity of the left eye two days later. He had not recovered at the time of the report. Concomitant medications included clomipramine, imipramine, fluphenazine, perazine, promethazine, fluspirilene, lithium, and nicergoline.

ARTERITIS (1)--One case of arteritis resulting in unilateral blindness was received from Ireland. A 64 y.o. female who was taking omeprazole 20mg/day (approximately 4 weeks) and oxprenolol (long term intermittent use) experienced headache and loss of sight in one eye associated with temporal arteritis, which partially resolved after omeprazole was discontinued and steroids administered. There was no recovery of visual acuity however.

RETINAL DETACH (1)--One Swedish case of retinal detachment was reported in a 69 y.o. male during an omeprazole study (20mg/day orally). Time to onset was reported as Day 79. He was hospitalized, reported to recover with the study drug continuing.

RETINITIS (1)--A 37 y.o. male (France) developed a "metaretinitis" after approximately 1371 days of omeprazole therapy (initially 40mg/day p.o., changed to 20mg/day at an unknown date) and Gelox® antacid. One of his eyes was surgically removed due to the presence of a "primitive metastatic tumor". He was later diagnosed with and died due to cancer of the esophagus. He had continued to take omeprazole until the time of death, 8 months after retinitis was diagnosed.

UVEITIS (1)--An 82 y.o. male (Austria) with a history of necrotizing pancreatitis with choledocholithiasis was given 2 doses of omeprazole 80mg/day (i.v.) then underwent endoscopic papillotomy and stone extraction 5 days later. Following this he was prescribed cefoxitin (7 days) and cilastin/imipenem (7 days). Five (5) weeks following his surgery, omeprazole 80mg/day i.v. was prescribed. Day 3 of this course of therapy, he experienced blurred vision for 2 days as well as "vision of black points". Day 5 omeprazole therapy was changed to 40mg/day p.o. On the same day he developed blindness. Exam at later date revealed left-sided iridocyclitis, as well as progressive cataract with opacity on both eyes. Omeprazole was discontinued on Day 19. Blindness persisted.

Other visual disturbances (9): BLIND 3, DIPLOPIA 2, AMBLYOPIA 1, VISION ABNORM 1, MYDRIASIS 1, VISUAL FIELD DEFECT 1.

Blindness was reported in 3 cases as the primary event. One case, a 73 y.o. male (Belgium) with a medical history which included myocardial infarction, cerebral infarction/CVA, and seizures and was on several other medications, experienced sudden bilateral loss of vision on Day 14 of omeprazole 40mg/day p.o. Omeprazole was discontinued on Day 17. CT scan was conducted and blindness was attributed to bilateral occipital ischemic lesions. Approximately one month later he died, likely due to a cerebrovascular accident. Swelling of an eye and blindness occurred in a 69 y.o. female (U.S.) with a history of cataract surgery 6 years prior who was taking omeprazole 20mg/day p.o. (time to onset unknown) and nifedipine. A "membrane" was removed from the back of her eye and vision was restored. Omeprazole therapy was continued. The third case of blindness (Spain) occurred in a 30 y.o. male with pancreatitis who was started on omeprazole 20mg/day p.o., clomethiazole edisialate, and tiapride hydrochloride on the same day. Day 2 of therapy he experienced blindness. Omeprazole was discontinued on Day 10; it is not known if the other 2 drugs were continued. Three weeks later, he had not recovered his vision.

Visual field defect was reported (Germany) in a 50 y.o. male on omeprazole 80mg/day p.o. (Days 1-10) and 40mg/day p.o. (Days 11-possibly 42), amoxicillin, and cisapride. On Day 15, he experienced visual field impairment "with increasing regression of

impairment after omeprazole withdrawal". As of approximately one month later, he had not recovered.

Mydriasis and pupils nonreactive to light were reported in a 19 y.o. male (U.S.) taking omeprazole p.o. (dose, duration unknown). Findings of mother (a nurse) were not confirmed by a physician.

Amblyopia was reported in 1 patient, a 69 y.o. male (U.S.) who experienced blurred vision, headache and pounding in his head like his heart was beating very hard, and "felt like he was having a stroke" on Day 1 of omeprazole 40mg/day p.o. Other medications included diltiazem, albuterol inhaler, simvastatin, and ferrous sulfate. Omeprazole was discontinued on Day 4, with a positive dechallenge reported.

Abnormal vision (NOS) was reported in 1 case from Germany. Total daily dosage was 20mg p.o., time to onset was 2 days, and a positive dechallenge was reported. Concomitant medications included albuterol, beclomethasone inhaler, prednisolone, indomethacin, nifedipine, carbamazepine, and temazepam.

Diplopia was reported in 2 cases (one domestic, one German). The German case was a 67 y.o. male who died of metastatic prostate cancer while on unspecified omeprazole therapy. He experienced symptoms which included ptosis and double vision that were thought to indicate that his cancer involved the CNS. The second case was a 20 y.o. male on omeprazole 20mg/day p.o. who developed diplopia after 4 to 6 weeks of omeprazole therapy. No further info was available.

Discussion

Most of the cases in this series were foreign (68%). Most patients were taking the oral dosage form alone (81%). Of the patients taking oral omeprazole (alone or with sequential IV use), the mean maximum daily dose administered was 33mg and median was 20mg (n=27). The mean maximum daily intravenous dose was 96 mg and median was 80mg (n=5). The time to onset of the first visual symptoms (regardless of dosage form used) varied widely (range 1 to 1371 days), although the median time to onset was 21 days (n=23). The mean age in this case series was 55 y.o. and median age 57 y.o.

The outcome of many of the cases in this series was of a serious nature: 5 patients were hospitalized or had an extended hospitalization, 11 experienced disability or persistent changes to their visual status, and 5 patients were in both categories. Sixteen (16) patients experienced permanent or unrelenting changes in visual status. Four (4) patients experienced a positive dechallenge after omeprazole was discontinued; these cases included one each of abnormal vision, change in shape of eye and lens, discolored contact lens, and amblyopia. Twelve (12) negative dechallenges were reported: optic atrophy (4), optic neuritis (3), arteritis (1), blindness (1), papilledema (1), uveitis (1), and visual field defect (1). Nineteen (19) cases specifically mentioned an ophthalmologic exam was conducted or were diagnosed with conditions which would have required an ophthalmologic exam.

Two possibly related conditions with generally serious outcomes, optic neuritis and optic nerve atrophy, had several reports (9 cases in total) in the SRS. However, 8 of these cases were confounded by preexisting conditions or were later attributed to other systemic conditions. One patient had preexisting optic atrophy, one was later diagnosed with an inflammatory demyelinating condition (acute neuromyelitis optica), and one with systemic

lupus erythematosus. Two (2) cases had a poor temporal association to use of omeprazole (2 to 3 years and 960 days). One patient had a complex medical history and MRI showed evidence of disturbed cerebral circulation, as well as an older cerebral infarction. Another patient had a history of smoking and was diagnosed with suspected intracerebral ischemia in the area of the visual pathway. Another patient experienced optic neuritis also thought to be related to smoking. The remaining case, optic neuritis Case 4, did not appear to be confounded.

There were several other conditions each of which had one case that was not obviously confounded: EYE DIS (change in shape of eye and lens, positive dechallenge), CATARACT (patient in his 30s), HEM RETINAL (55 y.o. female with hemorrhage in lower eye), UVEITIS (82 y.o. male), VISUAL FIELD DEFECT (50 y.o. male), AMBLYOPIA (positive dechallenge), VISION ABNORM (short time to onset, positive dechallenge), and DIPLOPIA (20 y.o. male). However most of these cases were also difficult to assess, given the usual prevalence of such conditions in the general population, the infrequency of reporting of these events to the SRS for omeprazole, and/or a lack of detailed clinical history in some cases which might reveal possible confounders.

Conclusion

This case series provides an update to a previous analysis of SRS reports of ophthalmologic events occurring in association with the use of omeprazole (Prilosec®) during the postmarketing period. This issue continues to be difficult to assess as to whether a possible relationship exists between omeprazole therapy and the occurrence of ophthalmologic events. A variety of conditions were represented (most of which have few cases of each), many cases were confounded by preexisting medical conditions, and a number had a poor temporal relationship with the use of omeprazole. We will continue to monitor these events as they are reported to the SRS for omeprazole.

[/S/]
Carol Pamer, R.Ph.

Concur:

[/S/]
Toni Piazza-Hepp, Pharm.D.
Group Leader

[/S/]
David Barash, R.Ph.
Branch Chief

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-180 M.Walsh/H.Gallo-Torres/S.Fredd
HFD-730 Acting Division Director
HFD-733 Acting Branch Chief/Wysoski
HFD-735 Barash/Piazza-Hepp/Pamer/Consult/Chron

Attachment E

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 13 1998

FROM: Carol Pamer, R.Ph., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Ralph Lillie, Acting Director 8/11/98.
Division of Epidemiology and Surveillance, HFD-730

TO: Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Omeprazole Ophthalmologic Disorders Update

A request was received from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) to provide a summary of reports in the FDA Spontaneous Reporting System of ophthalmologic disorders occurring during the use of omeprazole (Prilosec®, Astra Merck, USA). The purpose of this request was to prepare for a joint meeting with the Division of Over-the-Counter (OTC) Drug Products (HFD-560) held on April 8, 1998 at which an application for an OTC omeprazole product was discussed.

Note: These materials have previously been provided to the Division via email summary. This memorandum is provided for purposes of filing these reference materials to NDA 19810, Omeprazole (Prilosec®, Astra Merck).

Note that 2 previous consults have been completed at HFD-180's request regarding this issue (see Attachments 1 and 2).

SRS and AERS search results

To update these consults, the SRS and AERS were searched for any event with an ophthalmologic event where omeprazole was listed as suspect: SRS OPH% midlevel term, AERS "Eye Disorders" SOC term. As of April 28, 1998 a cumulative total of 159 reports were retrieved by searching both databases. Of these 159 reports, 78 were new cases received since the most recent consult completed (dated 10/12/1995, cutoff date 7/10/95). No cases were excluded to provide a summary of all suspected events. Note, therefore, confounding factors may be present in these cases.

DEMOGRAPHICS:
Number of cases, unless otherwise stated=78

Domestic cases: 49 (10 serious, 3 likely due to other conditions)
Foreign cases: 29 (all serious outcome)

Serious outcome indicated: 39
Nonserious or unknown outcome: 39

Dechallenge: Positive 19, Negative 21, N/A or unknown 38

Rechallenge: Positive 0, Negative 2, N/A or unknown 76

Sex: Female 45, Male 28, Not stated 5

Age (n=63): Mean 57.5 years, Median 58 years, Range 17 - 88 years

Dosage form administered: Oral 72, IV only 2, IV+Oral 2, Unknown 2

Daily dose (n= 53): Mean 34 mg, Median 20 mg, Range 10 - 360 mg

Time to onset (n=42, where specific info provided): Mean 177 days
Median 22 days
Range 1 - 1218 days

Table 1 (Attachment 3) provides a listing of the 78 ophthalmologic events where omeprazole was listed as the suspect drug that have been recently reported to the SRS and AERS databases.

[/S/]
Carol Pamer, R.Ph.

Concur:

[/S/]
Toni Piazza-Hepp, Pharm.D.
Group Leader

APPEARS THIS WAY
ON ORIGINAL

cc: HFD-180 NDA 19810
HFD-730 Acting Division Director (Lillie)
HFD-733 Acting Branch Chief (Rodriguez)/Wysowski
HFD-735 Barash/Piazza-Hepp/Pamer/Consult/Chron
HFD-737 Neal

Attachment 3: Cases of Ophthalmologic Disorders (Update)

Report #	Country	Year	Primary Ophthalmologic Event (Dx)	Outcome(s)	Dechallenge	Rechallenge	Sex	Age (Yrs)	Route	Daily dose (mg)	Time to onset (Days)
19970300165	US	1993	Amblyopia	Hospitalized			M	65	PO	20	90
19950100022	US	1994	Amblyopia			N/A	F	43	PO	10	700
19941200134	US	1995	Amblyopia				F		PO		60
19950700115	US	1995	Amblyopia				F		PO	20	
19970600147	US	1997	Amblyopia	Disability	Negative	N/A	F	55	PO	40	12
16/87442	France	1996	Blindness	Disability	Negative	N/A	F	44	IV		1
19951100096	US	1995	Blindness, seizures	Hospitalized			F	63	PO		
19951100102	US	1995	Blurred vision		Negative	N/A	F	38	PO	20	Almost immediate
19951000330	US	1995	Blurred vision		Positive	N/A	F		PO	20	
19951000329	US	1995	Blurred vision			N/A	F		PO	20	<56
JAUSA-23684	US	1996	Blurred vision		N/A	N/A	F	72	PO		
19970400011	US	1997	Blurred vision		N/A	N/A	F		PO		
19970400179	US	1997	Blurred vision		N/A	N/A	F		PO		
19970800022	US	1997	Blurred vision				F	65	PO	20	
19960900009	UK	1996	Blurred vision	Hospitalized	Positive	N/A	F	82	PO	40	29
19970400223	US	1997	Blurred vision, anaphylaxis	Hospitalized	N/A	N/A	F		PO	20	1
19941100045	US	1994	Cataracts bilateral	Disability	N/A	N/A	M	39	PO	80	337
19980200072	Foreign	1998	Cataracts bilateral	Disability	N/A	N/A	M	45	PO		14
19950300018	US	1995	Conjunctivitis		Positive	N/A	F	54	PO	20	1
19951100198	Japan	1995	Conjunctivitis/allergic reaction	Hospitalized	Positive	N/A	M	48	PO	20	Intermittent
19970900134	Sweden	1997	Conjunctivitis/vasculitis	Hospitalized	Negative	N/A	F	58	PO	20	619
19940400226	US	1994	Contact lens discolor		Positive		F	65	PO		5
19940500540	US	1994	Contact lens discolor		Positive	N/A	M	28	PO	20	Few days
19960200159	US	1995	Corneal erosion			N/A	M	44	PO	10	<2 years
19951100197	Netherlands	1992	Corneal lesion	Hospitalized	Negative		F	49	PO		2-3 yrs
19950500157	US	1995	Diplopia	Disability	Positive	N/A	F		PO	40	365
19960800087	US	1996	Diplopia				U		PO		
A0048496	US	1996	Diplopia		Positive	N/A	F	81	PO		
19970900004	US	1997	Diplopia	Disability	Positive	Negative	M	74	PO	20	

19970200054	US	1997	Diplopia		Positive	N/A	F	81	PO		
FDA M2043602	US	1997	Diplopia/inc DPH levels	Hospitalized	Positive	N/A	F	49	PO	20	30
19941200067	US	1994	Dry eye				F	44	PO	20	365
19941000059	US	1994	Dry eye				M	46	PO	20	1
19950200076	US	1995	Dry eye		N/A	N/A	U		PO		
19960400007	US	1996	Dry eye		Negative	N/A	F	57	PO	20	
19960400099	US	1996	Dry eye		Positive	N/A	F	78	PO	20	2
19960700145	US	1996	Dry eye				U		PO		
19960700129	US	1996	Dry eye				M	47	PO		<14
19960600099	US	1996	Dry eye				M		PO		
19960500050	Netherlands	1996	Extraocular paralysis	Hospitalized	N/A	N/A	U				
9601386	France	1996	Eye deviation	Hospitalized	Positive	N/A	M	65	IV	160	71
19960600039, 19960600126	US	1996	Eye pain		Positive	N/A	M	73	PO	20	34
19941100083	US	1995	Floaters				U		PO		
19950900043	US	1995	Focus abnormal				M	58	PO	20	12
19960400120	US	1996	Halo vision				F	63	PO	20	276
19961100102	US	1996	Intraocular pressure increased		N/A	N/A	M	44	PO	20	
19960800013	US	1996	Light in visual field		Positive	N/A	M	58	PO	20	6
19960400142	US	1996	Light in visual field		N/A	N/A	F	75	PO	20	<31
USA-23657	US	1993	Ocular pressure increased		N/A	N/A	F	40	PO		
-26795	Germany	1995	Optic atrophy	Hospitalized	Negative	N/A	M	54	PO	20	15
19970400298	France	1996	Optic atrophy	Hospitalized	N/A	N/A	F	41	PO	20	Years
19951000009	Portugal	1995	Optic nerve ischemia	Disability	Negative	N/A	F	71	PO	20	365
19951000156	Spain	1995	Optic neuritis retrobulbar	Disability	Negative	N/A	F	70	PO	20	699
19960100190	Germany	1995	Optic neuropathy	Disability	Negative	N/A	M	59	PO	40	
19960700164	US	1996	Photosensitivity				F	56	PO		
19970800019	US	1997	Ptosis eyelid				F		PO		
19961200134	UK	1996	Ptosis eyelid	Hospitalized	Positive	N/A	F	66	PO		
19941200036	France	1994	Ptosis eyelid	Disability			F	74	PO		
19971000005	Australia	1997	Retinal artery occlusion	Disability	Negative	N/A	M	69	PO	40	1218

19950500098	UK	1995	Retinal detachment	Hospitalized	N/A	N/A	M	74	PO	20	920
WAES94050461	Portugal	1994	Retinal detachment	Disability	Negative		M	61	PO	20	16
19980300041	Germany	1998	Retinal edema	Hospitalized	Positive	N/A	M	41	IV/PO	80	7
19950500102	Spain	1994	Retinal hemorrhage	Disability	Negative	N/A	F	54	IV/PO	360	10
19950500042	Norway	1994	Retinal pigment epithelium avulsion	Disability	Negative	N/A	M	54	PO	20	781
19950500006	US	1995	Retinal tear		Negative	N/A	M	43	PO	20	5
19950500102	France	1994	Retinal vascularity	Hospitalized	N/A	N/A	F	28			
19960800057	Australia	1995	Retinal vein thrombophlebitis	Disability	Negative	N/A	M	60	PO		
19960700155	Germany	1996	Retrobulbar neuritis	Hospitalized	Positive	N/A	F	61	PO	40	41
19971000010, 97-09-0860	US	1997	Scotoma	Disability	N/A	N/A	M	52	PO	20	38
19960200039	Denmark	1995	Vision decreased	Disability	Negative	N/A	M	79	PO	20	22
19960700095	US	1996	Vision loss		Positive	N/A	F	17	PO	20	15
19950200069	US	1995	Visual disturbance				F	52	PO	20	1
19960700068	Germany	1996	Visual disturbance	Hospitalized	N/A	N/A	F	70	PO	20	16
9980300567	Germany	1997	Visual disturbance	Disability	N/A	N/A	M	27	PO	40	
9960900019	France	1989	Visual disturbance	Hospitalized	Negative	Negative	F	88	PO	20	
FDA M1904624	US	1996	Visual disturbance/migraines		Negative	N/A	F	64	PO	20	38
19960200172	US	1996	Visual impairment	Hospitalized	Negative	N/A	M	75	PO	20	10
19951100033	Germany	1995	Visual impairment	Death MI	Negative	N/A	F	74	PO	40	5

Drug Attachment F

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 7/30/99

FROM: Lois La Grenade, M.D., M.P.H, Epidemiologist
Division of Drug Risk Evaluation I, HFD-430

Ann Corken, R.Ph., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation II, HFD-440

THROUGH: Evelyn Rodriguez, M.D., M.P.H., Director
Division of Drug Risk Evaluation II, HFD-440

TO: Lilia Talarico, M.D., M.P.H., Director, ODE III
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Consult: Review of medical literature and worldwide post-marketing reports for tumors associated with proton pump inhibitors, and suggestions for studies to be undertaken by sponsor.

This memorandum contains IMS trade secret data
For FDA internal use only
Do not release outside FDA

Introduction

This consult is in response to a request from Maria Walsh for a review of all postmarketing reports of tumors associated with the use of the proton pump inhibitors (omeprazole, lansoprazole, rabeprazole and pantoprazole) worldwide and in the medical literature, and suggestions for studies to be undertaken by the sponsor.

The proton pump inhibitors are a relatively new class of anti-secretory drugs generally in use since 1989 for treatment of acid-peptic disorders. They act by blocking the hydrogen-potassium adenosine triphosphate enzyme system at the secretory surface of gastric parietal cells. Omeprazole was approved by the FDA for use in the United States on 14th September 1989, and lansoprazole on 10th May, 1995. Pantoprazole and rabeprazole have not yet been approved by the FDA. Between 1995 and 1996 pantoprazole was launched in several countries including Europe, Australia, New Zealand and South America. Rabeprazole was launched in the United Kingdom and Germany in 1998 and in Sweden since the start of this year. The proton pump inhibitors

are indicated for the short term treatment of active duodenal ulcers, benign gastric ulcers, erosive esophagitis and for long term treatment of hypersecretory conditions, including Zollinger-Ellison syndrome.

Animal studies indicated that life-long treatment of rats with high dose omeprazole caused carcinoid tumors in the gastric fundus. Another concern was that prolonged achlorhydria might lead to an increased risk of gastric carcinoma, as happens in pernicious anemia. Hence the initial recommendation that proton pump inhibitors should be used only for short term treatment of peptic ulcers. Later studies on humans have so far failed to support an increased risk of gastrointestinal carcinoma.

The objectives of this review are: 1) to examine the FDA's Adverse Event Reporting System (AERS) for reports of tumors associated with the use of proton pump inhibitors, along with a review of the worldwide postmarketing experience, and 2) based on this review, to make recommendations as to possible studies to be undertaken by the sponsor.

Methods

AERS

We searched AERS on July 13, 1999 for reports of tumors associated with each proton pump inhibitor individually using the SOC (System Organ Class) term Neoplasms benign and malignant (including cysts and polyps). Because of the large numbers of reports for omeprazole, a sample of the domestic (US) reports consisting of reports of gastrointestinal neoplasms was printed and examined for duplications and accuracy of information. All reports were examined for the other drugs.

WHO

Information was requested from the WHO database for adverse events to drugs for all reports worldwide on all four proton pump inhibitors.

LITERATURE REVIEW

A comprehensive literature search was performed by the main medical library for all articles related to tumors in animals and humans associated with the use of proton pump inhibitors.

DRUG UTILIZATION DATA

Drug utilization data were obtained from IMS Health National Prescription Audit (NPA) and National Disease and Therapeutic Index (NDTI) databases, which provide computerized records from 1993 onwards.

Results

The results are summarized in Tables 1 – 5, Appendix.

AERS

Tables 1 and 2 give an overview of the AERS results. For omeprazole the total number of reported adverse events was 1499, of which 362 were neoplasm, benign and malignant. 343 of these neoplasms were US cases. Information on age and gender was available for 276 cases, 166 (61%) of whom were adult and 108 (39%) elderly. Forty-five percent were female.

For lansoprazole, the total number of reports was 227, with 46 neoplasms, benign and malignant, 13 of which were US cases. Of the 46 cases of neoplasms, 43 had information on age and gender. Seventeen (60%) were female and 26 (60%) male; 24 (56%) were adult and 19 (44%) elderly.

For pantoprazole there were 3 reports, two of which were listed as cancer related, both being foreign cases with pantoprazole as a concomitant drug. There were no reports for rabeprazole.

Image retrieval and sorting showed 85 reports associated with omeprazole use, 54 of which were unduplicated domestic reports of gastrointestinal neoplasms. Gastric polyps were the commonest (19 cases), followed by gastric cancer (14 cases) and gastric carcinoids (9 cases). For many reports information was incomplete and it was difficult to infer causality. For those for whom it was recorded, duration of use ranged from a few days to 10 years, with a median of 3 years. There were no domestic cases of gastric polyps, carcinoid, or gastric carcinoma for lansoprazole.

WHO

Table 3 summarizes the WHO results. Omeprazole, the first proton pump inhibitor to be launched world wide, had the largest number of all reports of adverse events, all neoplasms, all gastric neoplasms and other gastrointestinal neoplasms. There were 156 reports of neoplasms for all drugs (0.7% of all reports). Forty one (26%) of these were gastric carcinomas and 12 (9.6%) were other gastrointestinal malignant neoplasms (excluding liver, pancreas and gall-bladder). The largest number of reports of neoplasms with omeprazole was for the USA (111, 71%). Of the 41 gastric carcinomas, 34 (83%) were US cases.

DRUG UTILIZATION DATA

Projected total number of prescriptions for omeprazole and lansoprazole are shown in Table 4. The total number of prescriptions has steadily increased with each year on the market. Omeprazole (Prilosec) with —— prescriptions was the sixth most commonly prescribed drug in the USA in 1998 (The Top 200 Drugs. *American Druggist* February, 1999, pg. 43). Table 5 shows the age groups of users of the drugs. There was a slight female preponderance in use of the drug both in children and adults. Mean duration of therapy for omeprazole was 34 –36 days, depending on the age group, and 31–33 days for lansoprazole

LITERATURE

The following databases were searched: MEDLINE on PubMed, Life Sciences, Embase, IPA (International Pharmaceutical Abstracts) and Biosis (Biological Abstracts) for tumors associated with omeprazole, lansoprazole, pantoprazole and rabeprazole. More than 100 citations were found, only a few of which were actual case reports.

Review of the literature revealed that concerns about the carcinogenicity of proton pump inhibitors arose with omeprazole and the results of toxicological studies in rats, mice and dogs, which showed generalized hyperplasia of the gastric mucosa (1). Much of this hyperplasia was due to proliferation of gastric endocrine cells (enterochromaffin-like or ECL cells) (2,3). In rats only, life-long (2-3 years) administration of high doses of omeprazole induced gastric carcinoid tumors. Hypergastrinemia induced by prolonged administration of acid suppressing medication has also been shown to produce gastric carcinoids in *Mastomyces*, a sub-Saharan rodent genetically predisposed to developing carcinoids (4). Extreme acid suppression as occurs in proton pump inhibitor treatment, has since been shown to cause high levels of circulating gastrin (5,6), which in turn leads to a variety of hyperplasias in rodents, from dysplasia to neoplasia. Epidemiological studies so far have failed to show that this happens in man (7) but case reports have begun appearing of human gastric carcinoids occurring during long term use of proton pump inhibitors and H_2 receptor antagonists (8).

Burlinson et al in 1989 raised the possibility that omeprazole might be directly genotoxic, based on in vivo studies in rat gastric mucosa (9). Later studies failed to replicate this finding (10,11).

Based on the observation that patients with pernicious anemia develop gastric adenocarcinoma at a higher rate than the general population, it has been theorized that hypergastrinemia may cause gastrointestinal tract adenocarcinomas. However patients with Zollinger Ellison syndrome do not seem to develop gastric adenocarcinoma. (12). The other major physiological effect of gastrin is a trophic effect on gastrointestinal mucosa. Surgically induced hypergastrinemia is reported to increase gablet cell

proliferation in hamster colonic mucosa (13). Pinson and colleagues in 1995 reported an absence of trophic effects on colonic carcinoma in rats (14).

Powers and colleagues, in a 1995 review article on the possible carcinogenicity of gastric acid suppressing medications, concluded that "the relationship of gastric hyperplasia following prolonged administration of acid-suppressing medications to the generation of gastric malignancies remains unclear" (15). They made the point however, that increased cell proliferation generally leads to tumorigenesis in many systems, including gastrointestinal neoplasia and that gastrin might in fact be acting as a tumor promoter in the carcinogenesis process. In addition there have been reports of cancer developing in patients with Barrett's esophagitis on long-term omeprazole treatment (16).

In a retrospective study on the association between proton pump inhibitors and gastric polyps, Choudhry and his colleagues in 1998 concluded that long term use of proton pump inhibitors may be associated with the presence of small gastric fundic gland polyps and hyperplastic polyps (17). They recommended that a prospective study needed to be undertaken to investigate the matter further. One study on the long-term use of omeprazole showed no increase in gastric cancer risk and the investigators concluded that chronic use of proton pump inhibitors was safe (18).

A 1999 article on the safety profile of lansoprazole, which reviewed the results of short- (up to 8 weeks) and long- (up to 56 months) term clinical trials in 3281 participants, concluded that the safety profile of lansoprazole was similar to omeprazole (19). Results of clinical trials with rabeprazole and pantoprazole indicate that so far their safety profile is similar to omeprazole (20, 21).

Discussion

The majority of the cases reported in AERS did not show a clear temporal relationship between proton pump inhibitors and tumors, particularly malignant tumors like gastric carcinomas. Current knowledge of carcinogenesis indicates that a period of years, sometimes even decades is required between exposure to a carcinogen and development of the tumor (22). Proton pump inhibitors have been in general use in the USA for only 10 years. It is therefore too early to say with confidence whether there is an association between their use and cancer.

Possible Studies To be undertaken by Sponsor

In view of the remaining uncertainty as to whether or not there is an increased risk of gastrointestinal neoplasms with use of proton pump inhibitors further studies are needed. The best type of study design to answer questions of cancer risk are cohort studies – a group of people followed through time, with exposure measurements done at the start and follow up done at regular intervals to look for the outcome(s) of interest–in this case gastrointestinal neoplasms. However cohort studies are expensive–they take a very long time and require years of follow-up and are not suitable for studying rare events. For all

these reasons they are not always a practical pharmacoepidemiological tool for a drug regulatory agency, which must provide guidance on safety issues in a timely fashion.

We therefore suggest a compromise in which the benefits of a case control design–speed and relative cost efficiency–are combined with the advantages of a cohort study, reduced bias (recall, selection), and more complete ascertainment of outcomes/cases. We suggest that the sponsor undertake a case control study nested in an existing cohort. There are currently several large cohort studies in progress, the Nurses Health Study, the Health Professionals Follow-up Study and the Established Populations for Epidemiologic Studies of the Elderly (EPESE). Drug use data are currently collected every 2 years in EPESE and carcinogenicity studies have been published using information obtained from studying all these cohorts (23,24). Such a study would have the advantage of speed (the cohort is already established), reduced bias (exposure information–proton pump inhibitor use–can be collected prospectively from the entire cohort) and more complete case ascertainment as incident cases are collected. Incidence rates derived in this way could have internal comparisons with non-cases within the cohort and external comparison with incidence rates for gastrointestinal cancers in the US population in general. Drug usage data indicate that the drugs are used extensively in both adult and elderly populations. Study duration can therefore be shortened by using several cohorts simultaneously, providing relevant information can be collected. An adequate sample size can thus be studied to provide enough power to answer the study question–is the risk of gastrointestinal neoplasms increased by proton pump inhibitor use.

Conclusion

We conclude that the relationship between use of proton pump inhibitors and gastrointestinal cancer is not known, and recommend case control studies, nested in preexisting cohorts.

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[(S)]

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Attachments: Appendix

Copies: HFD-2 Lumpkin
HFD-400 Lillie
HFD-180 Houn/ NDA 19-810, 20-406, 20-973, 20-987
HFD-400 Garry (electronic copy/PID #99192)
HFD-440 Rodriguez/Corken /Piazza-Hepp/Epi files
HFD-430 La Grenade

Appendix

APPEARS THIS WAY
ON ORIGINAL

Table 1. Summary of AERS reports *

	Omeprazole	Lansoprazole	Pantoprazole
Total reports			
Total neoplasms			
GI Neoplasms (US)			

* Raw numbers, which may include duplicates.

Table 2. Age/Gender Distribution of AERS cases of Neoplasms with Omeprazole and Lansoprazole *

Drug	Omeprazole				Lansoprazole			
	Gender	Age Group		Total (%)	Gender	Age Group		Total (%)
	Female	Adult	69	123 (45)	Female	Adult	7	17(40)
		Elderly	54			Elderly	10	
	Male	Infant	1	151 (55)	Male		0	
		Adolescent	1				0	
		Adult	96			Adult	17	26 (60)
		Elderly	53			Elderly	9	
	Unknown	Adult	1	2				
		Elderly	1					
				276				43

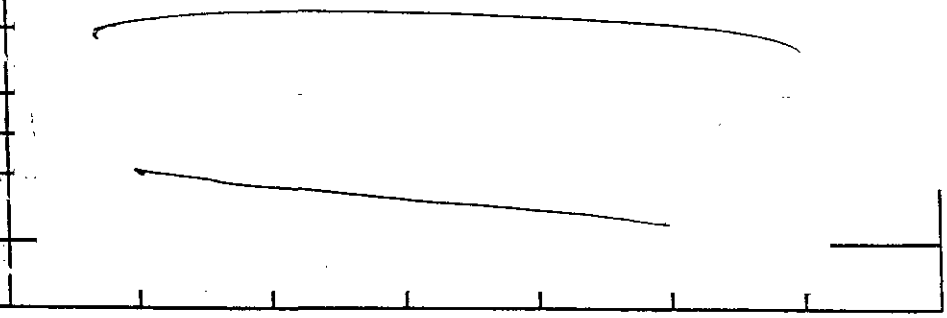
* Infant = age 0-2, adolescent 12-17, adult 18 – 66, elderly 66+

Table 3. Summary of WHO reports

	Omeprazole	Lansoprazole	Pantoprazole	Rabeprazole	Total
Total reports	17346	4826	785	124	23081
Total Neoplasms	144	6	6	0	156
Gastric Carcinoma	40	1	0	0	41
Other malignant GI Neoplasm	12	3	0	0	15

Table 4. Projected Total Prescriptions*

	Jan-May 1999 Total RX	1998 Total RX	1997 Total RX	1996 Total RX	1995 Total RX	1994 Total RX	1993 Total RX
OMEPRAZOLE							
PRILOSEC A-M							
LANSOPRAZOLE							
PREVACID TAP							
PREVPAC TAP							



* IMS Health NPA Database

Attachment G

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: OCT 15 1991

FROM: Min Chen, R.Ph., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Joyce Johnson, D.O., M.A., Acting director (for J. 10-15-91)
Division of Epidemiology and Surveillance, HFD-730

TO: Stephen Fredd, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Medication Error Reports from Prilosec/Prozac Mix-ups

This memo is to inform you of several reports of medication/dispensing errors secondary to Prilosec/Prozac name similarities. These include two reports from the Spontaneous Reporting System (SRS) and five reports from the Drug Quality Reporting System (DQRS). An article entitled, "Medication Error Reports, Watch Out for Possible Prilosec/Prozac Mix-ups", published in Hospital Pharmacy, Vol.26, September, 1991, also raised the issue to alert pharmacists and nurses of the potential problem.

Introduction

Omeprazole (Prilosec) was approved on 9/14/89 for the short-term treatment of active duodenal ulcer, gastroesophageal reflux disease (GERD)- severe erosive esophagitis and poorly responsive symptomatic GERD, and pathological hypersecretory conditions, e.g., Zollinger-Ellison syndrome. It is marketed by Merck, Sharp & Dohme. In 10/90 the originally approved trade name Losec was changed to Prilosec because of Losec/Lasix name similarities.

Fluoxetine (Prozac) was approved on 12/29/87 for the treatment of major depressive disorder. It is marketed by Dista Products Co., a division of Eli Lilly & Co.

SRS Case Reports

The two SRS cases with noticeable adverse reactions were reported by the physicians to the manufacturer. Both patients were incorrectly dispensed fluoxetine (Prozac) instead of omeprazole (Prilosec).

Case #737503 was a manufacturer 15-Day report submitted in ____ 1991. The event occurred in _____ It described a female patient for whom omeprazole 20 mg was prescribed, but fluoxetine (Prozac) 20 mg was incorrectly dispensed. She had a subsequent increase in gastrointestinal symptoms and was hospitalized. She was treated with unspecified prescription drugs and recovered.

Case #742441 was a manufacturer periodic report submitted in ____ 1991. The event occurred in _____ It described an 83 yo female who was placed on therapy with omeprazole for the treatment of esophagitis. Her esophagitis did not improve. Following two months of therapy, it was noted that the patient's prescription bottle had been inadvertently filled with fluoxetine (Prozac).

Summary of DQRS Case Reports

All 5 cases were reported by pharmacists for the product Prilosec. Three originated from the USP Drug Product Problem Reporting (DPPR) System. At least 2 events have been also reported to the manufacturer, according to the report.

None has indicated any serious outcome resulting from the problem in these 5 cases.

The following information is noted from the reports and obtained upon follow-up:

event location:	_____
date reported:	_____
prescription form:	telephone order(2), written order(2), unspecified(1)
dose taken:	1 dose(3), none(1), unspecified(1)

In summary, a medication dispensing error occurred in which Prozac 20 mg was dispensed instead of Prilosec 20 mg either from a telephone or written order. The reporters have noted confusion between Prilosec and Prozac in terms of the following problems:

1. The spelling is similar. Both products begin with the letter "P", end in letter "c", and are both in 20 mg capsules.
2. The handwriting of the name is similar.
3. The pronunciation is confusing via telephone order.
4. The dosing schedule AM is the same.

In one case, the reporter stated that prescriptions were seen written "Prozac, one in A.M. for stomach acid."

Conclusion

We have 7 case reports in the SRS and DQRS regarding medication/dispensing error resulting from Prilosec and Prozac mix-ups. In all cases, Prozac was incorrectly dispensed from written or telephone prescription orders. Two reports in the SRS had noticeable adverse reactions resulting from Prozac. The concerns from the reporting pharmacists had been that the two products, Prilosec and Prozac, have similar spelling, strength, and dosing schedule which increase the potential for dispensing/medication error for the health professionals.

Copies of the SRS and DQRS case reports, and the Hospital Pharmacy article are attached for your information.

C /S/ J
Min Chen, R.Ph.

Concurrence:

C /S/ J
Ann Tanner, R.Ph., M.P.H.
Group Leader, Reports Evaluation Branch

C /S/ J
David Barash, R.Ph.
Acting Chief, Reports Evaluation Branch

cc:
HFD-180, HFD-120/Leber
HFD-730/Johnson
HFD-733/Gross/Stadel
HFD/735/Barash/Tanner/Chen/Memo
MChen/10/7/91

Attachment H

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: DEC 19 1991

FROM: Min Chen, R.Ph., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Joyce Johnson, D.O., M.A., Acting Director /s/ 12-19-91
Division of Epidemiology and Surveillance, HFD-730

TO: Stephen Fredd, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Consult Request on Drug-Interaction Profile in the SRS for Omeprazole (Prilosec)

This memo responds to Dr. Gallo-Torres' Consult dated 10/9/91 requesting a drug-interaction adverse reaction profile between omeprazole and other drugs based upon the FDA Spontaneous Reporting System (SRS).

We searched the SRS under the COSTART term DRUG INTERACTION to identify cases that reported drug-interactions between omeprazole and any other drug(s). A total of 26 case reports involving 15 different drugs other than omeprazole were identified. Cases which were not reported as having a drug interaction adverse reaction will not be included in this report.

The drug-interaction profile of omeprazole is presented as follows. The line listing and copies of these 26 case reports are attached for your information.

Introduction

Omeprazole, marketed as Prilosec by Merck Sharp & Dohme, was approved on 9/14/89. It is a substituted [redacted] compound that inhibits gastric acid secretion by specific inhibition of the H^+/K^+ ATPase enzyme system at the gastric parietal cell surface.

It is indicated for the short-term treatment of active duodenal ulcer, gastroesophageal reflux disease (GERD)- severe erosive esophagitis and poorly responsive symptomatic GERD, and pathological hypersecretory conditions, e.g., Zollinger-Ellison syndrome.

In the labeling, the Drug Interactions subsection of the Precautions section states the following:

"Omeprazole can prolong the elimination of diazepam, warfarin and phenytoin, drugs that are metabolized by oxidation in the liver. Although in normal subjects no interaction with theophylline or propranolol was found, there have been reports of interaction with other drugs metabolized via the cytochrome P-450 system (e.g., cyclosporin, disulfiram). Patients should be monitored to determine if it is necessary to adjust the dosage of these drugs when taken concomitantly with Prilosec.

Because of its profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that omeprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts)."

Demographics

Of the 26 reports, 2 were foreign from Canada and France. There were nine 15-day, 2 direct and 15 periodic reports.

Report Year

	#cases	#serious	#death
90	16	6	0
91	10	3	1
sum	26	9	1

Age

Ages	#cases	#serious	#death
20-29	1	0	0
30-39	2	1	0
40-49	5	2	0
50-59	4	1	0
60-69	5	3	1
70-79	1	1	0
N/A	8	1	0

Sex

	#cases
female	13
male	10
N/A	3

Dechallenge/rechallenge

	#cases	#serious	#death
dechallenge	8	3	0
N/A	16	4	1
rechallenge	2	2	0
(dechallenge	9	after hands-on review correction)	

Drug-Interaction Profile

The profile of these 26 case reports will be divided into two sections in chart form. One is for those drugs that are known to interact with omeprazole (labeled), and the other is for drugs that are not known to interact with omeprazole (unlabeled). The emphasis will be on the unlabeled section.

Labeled

drug name	#cases	serious	dechall /rechall
cyclosporin	3	yes (1)	yes (2) /yes (1)
diazepam	0		
disulfiram (Antabuse)	1	yes (1)	yes (1) /yes (1)
phenytoin	0		
warfarin	2		

Unlabeled

Drug name	#cases & control#	serious	onset **	dechall ***	ADRs & comments
1. carbidopa-levodopa (Sinemet)	(4) 762144, 761407, 756933, *700279	yes (1)	2 mo(1) N/A (3)		kidney func abnorm parkinson synd.
2. lovastatin (Mevacor)	(3) 762180 674716 655061		2 wk(1) 2 mo(1) N/A (1)	yes (1) after F/U	cholesterol inc.
3.theophylline	(3) *737531 700231 677687	yes (1)	1-15 d	yes (1)	theophylline inc. toxicity- N/V, syncope
4. prednisone	(1) *701805	yes (1)	4 d	yes (1)	skin eruption, pruritus
5. prednisone & Motrin	(1) *643630	yes (1)	7 d	yes (1)	severe joint inflammation
6.carbamazepin (Tegretol)	(1) 676539		7 d	yes (1)	ataxia, nystagmus drug level inc.
.fluoxetine (Prozac)	(1) 761409		1 mo.		depression worsening
8.flurazepam (Dalmane)	(1) *712403	yes (1)	9 d	yes (1)	hallucination, confusion, creatinine inc
9.glyburide (Diabeta)	(1) 765040			yes (1)	hyperglycemia
10.lithium	(1) 700212		4 d	yes (1)	level inc from 1.3 to 2.4
11.nicardipine (Cardene)	(1) *737325	yes (1)	27 d		cardiac arrest & died (see case)
12.phenelzine (Nardil)	(1) 689537		1 dose		headache
13.rifampin	(1) *726265	yes (1)			no drug effect

* 15-day report
** onset: Omeprazole therapy duration when reaction(s) occurred.
*** There was no rechallenge information in these cases.

Summary

The drug-interaction profile of omeprazole from the FDA SRS indicates that there were 2 cases involving warfarin, 3 cases with cyclosporin, and 1 case involving disulfiram associated with interacting with omeprazole. These 3 drugs, which have been labeled for drug-interaction with omeprazole, are highly protein-bound (>90%) and metabolized by the liver.

The profile also indicates that several other drug interactions were reported after omeprazole was added to the patients' drug regimen. Thirteen drugs were involved in 20 case reports, in which 9 cases had a positive dechallenge after omeprazole was discontinued. The 9 drugs involved in these 9 cases are: carbamazepine, carbidopa-levodopa, flurazepam, glyburide, lithium, lovastatin, prednisone, prednisone with Motrin, and theophylline. Except lithium which is excreted in urine and not protein-bound, the rest of the drugs are primarily metabolized in the liver and also are highly protein-bound (56-99%) in the plasma.

Only 5 reports provided laboratory data to document the significant drug level changes before and after omeprazole therapy. Of these cases, 3 had increased theophylline levels up to 3 times baseline with significant toxicity after 1, 5 and 15 days of omeprazole therapy respectively. One case had an increase of carbamazepine to 3 times the normal level after 7 days of omeprazole and showed adverse effects such as ataxia and nystagmus. Another case indicated an increase of lithium level from 1.3 to 2.4 after 4 days therapy of omeprazole.

Drugs can interact at any point from the time of administration to the process of elimination. From the omeprazole drug-interaction profile, it is not known whether drug absorption was accelerated when omeprazole altered the pH of stomach acid or whether omeprazole displaces other drugs and causes an increase of free concentrations of displaced drugs resulting in potentially increased untoward effects, since omeprazole is approximately 95% protein-bound in the plasma.

Omeprazole has been shown to decrease several liver cytochrome P450-mediated monooxygenase activities both in vitro and in vivo. Therefore, omeprazole has some propensity for drug interaction, i.e., to decrease the metabolism of any drug specifically oxidized by a cytochrome enzyme.

[/S/]
Min Chen, R.Ph.
Acting Group Leader

Concurrence:

[/S/]
David Barash, R.Ph.
Acting Chief, Reports Evaluation Branch

cc:
HFD-180
HFD-700/Anello
HFD-730/Johnson
HFD-733/Gross/Stadel
HFD/735/Barash/Chen/Consult/Chron
MChen/10/28/91/12/5/91

APPEARS THIS WAY
ON ORIGINAL

Attachment I

DRU 1.7
Omeprazole

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration

MEMORANDUM

Center for Drug Evaluation and Research

CONFIDENTIAL

Date: 15 October 1992

From: Epidemiologist, HFD-733

Thru: Acting Director, HFD-730
Division of Epidemiology and Surveillance /s/ 10-19-92

To: Director, HFD-180
Division of Gastrointestinal and Coagulation Drug Products

Subject: Endocrine adverse effects of omeprazole

In response to your consult request for comment on the BMJ article, "Endocrine adverse effects of omeprazole," the following data from FDA's Spontaneous Reporting System (SRS) was tabulated. Table 1 contains information obtained from 22 reported cases of endocrine adverse drug events (ADEs) for the drug omeprazole. There were 6 reports of impotence and 11 of gynecomastia or breast enlargement. Three patients experienced breast pain and 2 galactorrhea without gynecomastia or breast enlargement reported.

Impotence: Four of the 6 cases of impotence were in men between 34 and 60 years (mean 49.25 years); 2 did not report age. Of the 6 patients, 3 were taking no concurrent drug therapy, 1 was on Darvocet and unspecified antibiotics; there were no concurrent medication data given for the other 2 cases. Three of the 6 were taking 20 mg of omeprazole daily, the other 3 did not report a total daily dose. Reflux disease was the indication for half of the men, one was being treated for a duodenal ulcer and another for Barrett's esophagitis. The diagnosis was not recorded in one case.

Gynecomastia: Eight cases of gynecomastia in men were reported. Of those with recorded ages, there was a range from 44 to 86 years (mean 66.6 years). Five of these patients took doses of omeprazole of 20 mg daily or every other day (including 1 on an intermittent regimen of 20 mg qd). Daily doses were not reported for the remaining 3 cases. Known indications for omeprazole therapy included esophageal reflux (1), esophagitis (2) and epigastric pain (1). The patient on the intermittent regimen experienced symptoms after 30 doses. Three of the men were taking 2 or more additional medications (see Table 1), 2 took none and there was no report of additional drug use by the remaining 3 patients. Among the men with reported onsets of reaction, there was a range from a possible 14 days to 124 days before gynecomastia was seen.

Breast Enlargement: There were 3 reports of breast enlargement in women ranging in age from 32 to 50 years (mean 43.3 years). Two of the 3 took an omeprazole daily dose of 20 mg (one intermittently), while the daily dose for the third patient was not reported.

Indications for therapy included reflux disease, reflux esophagitis and esophageal spasm. Two of the women were taking concurrent medications; one received terbutaline and the other an unspecified steroid injection. Onset of reaction was variable. One woman experienced breast enlargement on the first day of therapy while another (on an intermittent regimen of 20 mg qd for 4 days prn) experienced the reaction 73 days after initiation of therapy.

Breast Pain: A total of 3 women and 2 men experienced breast pain. Two patients experienced this as the only reaction (one male and one female); it was accompanied by gynecomastia or breast enlargement in 2 patients and by HTN and dizziness in the remaining woman. The age range was from 35 to 80 years (mean 55.0 years). The known data on concurrent medication use reveals 1 patient was on verapamil, 1 was taking ranitidine and hydroxyzine and 2 patients took no other medications. Known omeprazole doses were all initiated at 20 mg daily, although one patient was increased to 20 mg bid and another was decreased to 10 mg daily. Onset of reaction varied from 1 day to 417 days. Indications known for 3 patients were reflux disease (2) and prophylaxis against reflux esophagitis (1).

Using the data from the first three full years of marketing for each drug, tables 2 and 3 compare omeprazole with the H_2 antagonists with respect to the number of ADEs and new and total Rx reporting rates for impotence and gynecomastia respectively. The reporting rates for omeprazole are comparable to those of the H_2 antagonists for both reactions as well as for both methods of reporting rate calculation.

Tables 4 and 5 list total SRS reports for impotence and gynecomastia respectively by generic entity including omeprazole, the H_2 blockers, spirololactone, methyldopa, propranolol and verapamil. Three of these drugs were marketed before the SRS was established. In both Table 4 and 5, omeprazole has the fewest reports in the SRS. This is due, in part, to the fact that it is the newest of the drugs listed. The number of outpatient prescriptions dispensed for omeprazole by year since its introduction in 1989 are listed in Table 6.

Some limitations of the SRS data are as follows:

1. Causality for the reports has not been assessed and cannot be assumed. The drug may or may not actually be related to the adverse experience reported.
2. A determination of incidence cannot be made from these data.
3. Due to the voluntary reporting of these cases, many experiences/reactions may not be reported and some may be reported more than once from the same or different sources.
4. Occurrence rates and estimates of drug risk cannot be assessed based on these data alone due to duplicate reporting and/or under-reporting.

If there are any questions about these data, please contact me. Lisa Minecci, a pharmacy extern, has prepared the tables for this memo. You may contact her before October 30.

Laurie Burke, R.Ph., M.P.H.

Concur: [/S/] 10-19-92

Joel Freiman, M.D., M.P.H.
Chief, Epidemiology Branch, HFD-733

cc: HFD-733 DRU1.7omeprazole, Chron, Burke, Baum, Burkhart, Minecci
HFD-701 Anello
HFD-735 Chen
HFD-180 D. Yaplee

TABLE 1 (Source: FDAs SRS)
ENDOCRINE ADVERSE EFFECTS OF OMEPRAZOLE BY CASE

Case No.	Age and Sex	Reaction	Report Source	Onset date	Dose	Duration of Therapy	Duration of Therapy Before Reaction Onset	Indication	Other Drugs	Outcome	Possibly same as BMJ case#*
1	34, M	impotence, decreased libido	individual		20mg qd	34 days	7 days	Barrett's esophagitis	none	unknown	14
2	507, M	impotence	physician via manufacturer		20mg; total daily dose unknown	continued	unknown	duodenal ulcer	unknown	therapy continued, otherwise unknown	none
3	53, M	impotence	health care professional		20mg qd	21 days	unknown	G.E.R.D.	none	therapy stopped; positive dechallenge; recovery	15
4	607, M	impotence	physician via manufacturer		20mg qd	unknown	unknown	reflux disease	none	recovery	13
5	unknown age, M	impotence	physician via manufacturer		unknown	unknown	unknown	G.E.R.D.	unknown	unknown	none
6	unknown age, M	impotence	physician via manufacturer		unknown	unknown	unknown	unknown	unspecified antibiotics, propoxyphene napsylate/APAP	unknown	none
7	80, M	gynecomastia (and unilateral breast pain)"	RPh via manufacturer		20mg qd	(14 days)	approximately 2 months (14 days)	unknown	ranitidine, hydroxyzine, Ensure liquid food supplement	(therapy stopped; reaction resolved in 1-2 months)	none
8	84, M	bilateral gynecomastia, right breast mass, (left breast carcinoma)	physician via manufacturer		20mg qd for 8 (to 12) weeks then 20mg qod	14 months	approximately 1 year	esophagitis	metoclopramide HCl, sucralfate	hospitalization; left breast mastectomy; therapy continued	none
9	65, M	unilateral gynecomastia	physician via manufacturer		intermittent therapy, 20mg qd	3 months?	unknown; took 30 doses total	esophageal reflux	none	unknown	30
10	(44), M	bilateral gynecomastia	physician via manufacturer		(20mg qd)	(7 months?)	(1 to 2 months?)	erosive esophagitis	none	therapy continued (until December 1991); reaction gradually decreased	none
11	58, M	bilateral gynecomastia, left breast mass	physician via manufacturer		unknown	8 months	unknown	unknown	unknown	unknown	none
12	unknown age, M	gynecomastia	Pharm D via manufacturer		20mg qd	61 days? (124 days)	61 days? (124 days)	(epigastric pain)	famotidine, cimetidine, sucralfate, choline Mg trisalicylate, calcium carbonate, oxycodone/APAP, KCl, multi-vitamins, docusate Na, pancrelipase, metoclopramide HCl	therapy stopped; positive dechallenge; later rechallenge without recurrence	none

13	unknown age, M	gynecomastia	RPh via manufacturer	unknown	unknown	unknown	unknown	unknown	unknown	none
14	unknown age, M	gynecomastia	Pharm D student via manufacturer	unknown	unknown	unknown	unknown	unknown	unknown	none
15	50, F	breast enlargement	physician via manufacturer	20mg qd	unknown	unknown	unknown	terbutaline sulfate	therapy stopped; reaction persisted	none
16	32, F	breast and parotid enlargement	physician via manufacturer	20mg; total daily dose unknown	continued	73 days; repeatedly on day 1 of the 4 day prn regimen	esophageal spasm; 4 day prn regimen	unspecified steroid injection	therapy continued despite reaction	none
17	48, F	bilateral breast enlargement and pain	physician via manufacturer	20mg qd	3 days	1 day	reflux esophagitis	none	positive dechallenge and rechallenge; recovery	none
18	35, F	bilateral breast pain	physician via manufacturer	20mg qd initially, then 20mg bid	several months	unknown	reflux disease	verapamil HCl	unknown	none
19	unknown age, M	breast pain	physician via manufacturer	unknown	5 months?	5 months?	unknown	unknown	therapy stopped; positive dechallenge	none
20	57, F	hypertension, dizziness and breast pain	manufacturer; study report	20 mg qd for 1 month, then 10mg qd	continued	417 days	prophylaxis against reflux esophagitis	none	hospitalization; therapy begun for HTN; omeprazole therapy continued	none
21	55(49), F	galactorrhea	physician via manufacturer	20mg qd	(20 days)	2 weeks (19 days)	(reflux esophagitis)	unknown	(positive dechallenge; therapy restarted without recurrence)	none
22	(42), F	bilateral galactorrhea (and depression)	physician via manufacturer	(40mg bid)	(40 days)	(40 days)	(G.E.R.D)	ranitidine (none)	therapy stopped; positive dechallenge (in 2 weeks)	none

*M Lindquist, I Edwards. British Medical Journal 1992;305:451-2.
**Additional or conflicting information obtained from follow-up reports is shown in parenthesis.

TABLE 2 (Sources: FDAs SRS and NPA, IMS America)
IMPOTENCE (First 3 full years post marketing)

DRUG	# ADEs	TOTAL Rxs (in millions)	REPORTING RATE (#ADEs/million total Rxs)	NEW Rxs (in millions)	REPORTING RATE (#ADEs/million new Rxs)
omeprazole (10/89-9/92)	6				
cimetidine (8/77-12/80)	12				
ranitidine (6/83-12/86)	28				
famotidine (11/86-12/89)	6				
nizatidine (5/88-12/91)	16				

TABLE 3 (Sources: FDAs SRS and NPA, IMS America)
GYNECOMASTIA (First 3 full years post marketing)

DRUG	# ADEs	TOTAL Rxs (in millions)	REPORTING RATE (#ADEs/million total Rxs)	NEW Rxs (in millions)	REPORTING RATE (#ADEs/million new Rxs)
omeprazole (10/89-9/92)	10				
cimetidine (8/77-12/80)	30				
ranitidine (6/83-12/86)	42				
famotidine (11/86-12/89)	18				
nizatidine (5/88-12/91)	17				

TABLE 4
TOTAL ADE REPORTS OF IMPOTENCE BY DRUG

DRUG (year marketed)	TOTAL SRS: 2867 cases (100%)
cimetidine (1977)	179 (6.2%)
verapamil (1981)	97 (3.4%)
ranitidine (1983)	72 (2.5%)
methyldopa (1963)	68 (2.3%)*
propranolol (1967)	66 (2.3%)*
spironolactone (1963)	24 (0.8%)*
nizatidine (1988)	20 (0.7%)
famotidine (1986)	12 (0.4%)
omeprazole (1989)	6 (0.2%)

Source: FDA's Spontaneous Reporting System
*The SRS was established in 1969, complete data are unavailable.

TABLE 5
TOTAL ADE REPORTS OF GYNECOMASTIA BY DRUG

DRUG (year marketed)	TOTAL SRS: 1882 cases (100%)
cimetidine (1977)	337 (17.9%)
spironolactone (1963)	191 (10.2%)*
ranitidine (1983)	82 (4.4%)
methyldopa (1963)	73 (3.9%)*
propranolol (1967)	42 (2.2%)*
verapamil (1981)	39 (2.1%)
famotidine (1986)	27 (1.4%)
nizatidine (1988)	21 (1.1%)
omeprazole (1989)	10 (0.5%)

Source: FDA's Spontaneous Reporting System
*The SRS was established in 1969, complete data are unavailable.

TABLE 6
OMEPRAZOLE USE
Prescriptions Dispensed by Retail Pharmacies
Source: NPA, IMS America

YEAR	R_Xs DISPENSED (in millions)
1989	
1990	
1991	
1992	

• APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

I-4

TO (Division/Office)		FROM:		
HFD-730 (MIN CHEN)		HFD-180 (D. YARLEE)		
DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
9/9/92		19-810	JOURNAL ARTICLE	8/22/92
NAME OF DRUG		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
PRILOSEC (OMEPRAZOLE)				—

NAME OF FIRM

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY _____
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(Specify below)*

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW	☐ CHEMISTRY
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER
☐ OTHER	

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN–VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS *(List below)*
- ☐ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAF
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS *(Attach additional sheets if necessary)*

PLEASE REVIEW AND COMMENT ON "ENDOCRINE ADVERSE EFFECTS OF OMEPRAZOLE" FROM BMJ, VOL. 305, 8/22/92.

9-9-92
ENTERED
J.J.

SIGNATURE OF REQUESTER

METHOD OF DELIVERY *(Check one)* ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

Attachment 3

OMEPRAZOLE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Date: JAN 28 1992

From: Medical Officer,
Epidemiology Branch, DES, HFD-733

Through: Acting Director,
Division of Epidemiology and Surveillance, HFD-730 /s/ 1-24-92

Subject: CONSULT: Hepatotoxicity reports for omeprazole and H_2 blockers

To: Hugo Gallo-Torres, MD
Division of Gastrointestinal and Coagulation Drug Products, HFD-510

CONTAINS TRADE SECRET DATA - DO NOT RELEASE

This memorandum replies to your request for consultation dated 10/9/91 about differences among the following agents with respect to reports of hepatotoxicity: omeprazole, Tagamet®, Zantac®, Pepcid®, and Axid®.

As we discussed, a fair comparison would have to be limited to a comparable time period in the marketing history of each drug. The first three years are generally considered the optimal time to study as reporting rates drop off markedly afterwards. Since omeprazole was not licensed in the U.S. until 9/89, we determined the number of spontaneous, domestic reports received by the FDA Spontaneous Reporting System through the second full year of marketing for these drugs.

As you suggested in your 11/1/91 note, we focused on the most serious COSTART terms in which you expressed interest. ("Liver injury" was not included because there is no COSTART term for it.) The number of domestic spontaneous reports received for omeprazole is shown in the middle column of Table 1; none was received for the H_2 blockers. The last column shows the number of reports remaining after the following exclusions were made: the two hepatic encephalopathy cases appear to be duplicates, the fatal liver failure case was excluded due to confounding by alcoholism and a history of two episodes of hepatitis with jaundice prior to four to five months of omeprazole therapy, and two of the hepatic necrosis cases were duplicates. In addition, it should be noted that one of the hepatic necrosis cases had a history of chronic hepatitis B with "relatively stable hepatic dysfunction"; his bilirubin was 10 one day after his first dose of omeprazole and later increased to 20 (pre-treatment levels were not reported). Another was taking ibuprofen and had a biopsy revealing focal parenchymal necrosis along with patchy mild to moderate acute cholangiolitis and moderate intrahepatic cholestasis. Since one report was coded as both hepatic necrosis and liver failure, there are a total of seven unique reports for omeprazole.

Reporting rates were estimated by dividing the total number of reports for the COSTART terms in Table 1 by the estimated number of prescriptions dispensed from the time each drug was introduced

Table 1. Reports occurring during first two years of marketing of omeprazole		
COSTART terms	Total number of reports received	Number of reports after review
Coma Hepatic	0	0
Hepatic Encephalopathy	2	1
Liver Damage	0	0
Liver Failure	4 (including 1 death)	3 (3 hospitalized, no deaths)
Liver Necrosis	5	4 (1 death)

Table 2. Reporting rates, first two years of marketing					
	Tagamet	Zantac	Pepcid	Axid	Prilosec
	cimetidine	ranitidine	famotidine	nizatidine	omeprazole
Date Licensed	8/77	6/83	10/86	4/88	9/89
Number of Unique Reports	0	0	0	0	7

The reporting rate for omeprazole exceeds the upper limit of the confidence intervals for each of the H_2 blockers. While this may serve as a signal suggesting a possible important causal association, especially since one of the cases was fatal, the small number of reports involved (seven) and the many limitations of spontaneous reporting data make it necessary to exercise caution when interpreting these findings. Reviewing data from other sources would be helpful before concluding from these results alone whether omeprazole has a higher risk of hepatotoxicity than the other agents studied. We are in the process of determining whether any additional information could be obtained concerning this from the data sets available through our cooperative agreements.

You mentioned that you would like to see the results of this search before deciding whether to pursue an analogous comparison involving less serious terms. We will defer pursuing this until you have a chance to review these findings (as well as the separate memo Min Chen will send you concerning all reports received on the COSTART terms above since each drug came on the market.) If there is any other information you would like concerning this issue, please do not hesitate to call me at 443-2306.

[/S/]

Steven C. Kaufman, MD, MS

Concur: /S/

Epidemiology Branch Chief [/S/]

Copies:

HFD-700 Anello
HFD-730 Johnson
HFD-733 Kaufman/Chron
Dru 1.7 omeprazole
HFD-735 Chen
Kaufman/sck/1-2-92/443-2306
\projects\omeprazo\gallo.wp

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office): HFD-735 EPIDEMIOLOGY (MIN CHEN)	FROM: HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
10/9/91		19-810	[illegible]	[illegible]

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Prilosec			1/92

NAME OF FIRM: Merck Sharp & Dohme Research Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY ______
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☒ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER (Specify below)

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

- ☐ TYPE A OR B NDA REVIEW
- ☐ END OF PHASE II MEETING
- ☐ CONTROLLED STUDIES
- ☐ PROTOCOL REVIEW
- ☐ OTHER

STATISTICAL APPLICATION BRANCH

- ☐ CHEMISTRY
- ☐ PHARMACOLOGY
- ☐ BIOPHARMACEUTICS
- ☐ OTHER

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILITY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL– BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☒ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☒ COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFET
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

RE: Anti-ulcer drugs and ADRs related to the liver

Please search for liver ADRs in association with Tagamet, Zantac, Pepcid and Axid. In a fashion similar to recent research for OME + liver, please search under the terms hepatitis, liver necrosis, hepatic failure, hepatic coma, acute fulminant hepatitis, hepatic encephalopathy and related terms. Please clearly identify those instances (if any) where the liver damage was irreversible, culminating in the death of the patient. To compare this information with that recently gathered for OME, data on drug usage (total population exposure) would be appreciated.

SIGNATURE OF REQUESTER: C /S/ J x0479	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER: C /S/ J	SIGNATURE OF DELIVERER: C /S/ J

BEST POSSIBLE COPY

Attachment K

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: APR 02 1993

FROM: Evelyn R. Farinas, R.Ph.
Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Joyce Johnson, D.O., M.A., Acting Director
Division of Epidemiology and Surveillance, HFD-730

/S/ 4-1-93

TO: Stephen Fredd, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Monitored Adverse Reaction (MAR) Report
Drug: Omeprazole (Prilosec®)
Reaction: Acute Interstitial Nephritis

Omeprazole was approved in September of 1989 as a delayed-release capsule and is marketed by Merck & Co, Inc. under the trade name Prilosec®. This drug is indicated for the short term treatment of gastroesophageal reflux disease and for the long term treatment of pathological hypersecretory conditions. Omeprazole inhibits the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell, effectively blocking the last step in the production of gastric acid.

Prilosec® is absorbed in the intestine, metabolized in the liver, and eliminated in the urine as at least 6 metabolites. A small percentage of omeprazole doses has been found in the feces, suggesting that there is some biliary excretion as well. Bioavailability of oral omeprazole increased significantly in hepatic disease, and to a lesser degree in chronic renal disease. In the elderly, the elimination rate of omeprazole was somewhat decreased and bioavailability increased.

Daily dosage varies according to the disease being treated. Doses of 20 mg daily for 4 to 8 weeks are recommended for the treatment of active duodenal ulcer and GERD. Doses for adults having hypersecretory conditions vary according to the individual needs. The recommended adult dose is 60 mg daily, but doses as high as 120 mg three times a day have been administered.

Labeling:

Under the Urogenital subheading of the Adverse Reactions section, the labeling mentions the following: urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain, and gynecomastia. Fever and pain are mentioned under the subheading Body as a Whole, and rash is mentioned under the subheading Skin and under adverse events experienced by the clinical trial population. There is no mention in the current labeling of acute interstitial nephritis (AIN).

Acute Interstitial Nephritis:

AIN is usually associated with an abrupt deterioration in renal function and characterized by inflammation and edema of the renal interstitium. The symptoms may vary from subtle changes in the glomerular filtration rate (GFR) and tubular function, to profound renal failure requiring dialytic support. AIN has been associated with systemic infections in the past, but the most common cause now is related to the use of medications. Over 75 drugs have been implicated as etiologic agents. (See Appendix One). Idiopathic AIN has been reported less frequently and is not related to infections or drugs.

The clinical manifestations of drug-induced AIN depend on the medication producing the adverse renal reaction. Eosinophiluria is the urinary finding most suggestive of drug-induced AIN. AIN associated with B-lactam antibiotics occurs after several weeks of therapy, and is characterized by fever, rash, and eosinophilia. Heavy proteinuria is frequently seen in the clinical picture of AIN associated with non-steroidal anti-inflammatory drugs, together with minimal-change nephrotic syndrome. The onset of the nephrotic syndrome usually coincides with the onset of acute interstitial nephritis and acute renal failure. Discontinuation of the drug results in spontaneous remission of the nephrotic syndrome and the acute renal failure. Other drugs, such as rifampin, allopurinol or diphenylhydantoin may exhibit more generalized systemic allergic reactions.

The hypersensitivity picture of rash, fever and eosinophilia and the urinary finding of hematuria point to a probable diagnosis of AIN. Urinary eosinophiluria is useful in establishing the diagnosis of AIN since this has been found rarely in other cases of acute renal failure. However, a conclusive diagnosis of AIN can be made only from renal biopsy.

Selection of Cases:

We searched the FDA Spontaneous Reporting System [SRS] under the mid-level COSTART term RENALGLOM, which includes 9 COSTART terms, and under the individual COSTART term NEPHRITIS for cases of AIN associated with omeprazole. Both searches revealed the same 11 unduplicated cases.

All of the 11 case reports were COSTARTED as NEPHRITIS, in which 7 identified the adverse events as interstitial nephritis. Of the remaining 4, follow-up information revealed that the correct diagnosis was glomerulonephritis in 2 (#724512 and #781316), and interstitial cystitis and Goodpasture's syndrome in the remaining 2 (#742358 and 785098).

Of the 7 cases reporting interstitial nephritis, 3 were not included in this MAR document. In case # 884155, follow-up with the reporter indicated that the renal complications were the result of a high dose of methotrexate accompanied with insufficient alkalinization. Case # 642508 was confounded by the concomitant administration of erythromycin, which has been associated with interstitial nephritis. Furthermore, the reporter in this case indicated that the adverse events did not abate upon discontinuation of omeprazole and that these events could be the result of either drug. In case #882694, the patient continued receiving omeprazole therapy in spite of the development of interstitial nephritis. This foreign report provided no further details.

Therefore, a total of 4 cases of interstitial nephritis associated with omeprazole will be presented in this document. Copies of the cases are attached for your information.

Demographics:

sex:	female (3), male (1)
age:	mean (72.7), range (62-86)
daily dose:	40 mg (3), 20 mg (1)
time to onset:	10 days (1), 13 days (1), 2 months (1), 6 months (1)
dechallenge:	positive (3), unknown (1)
rechallenge:	positive (2), unknown (2)
outcome:	hospitalization (3), unspecified (1)
location:	domestic (3), foreign (1)
report year:	1993 (1), 1991 (2), 1990 (1)
report type:	15-day (4)

Summary of Cases:

The cases are summarized in Tables 1-4, starting on page 5.

Discussion :

Drug induced AIN is usually associated with symptoms of fever, rash, eosinophilia and renal failure. It can be confirmed by a renal biopsy. In this case series, not every patient had the classical symptoms of AIN. With the exception of case #4, in which detailed information was not available, however, at least 2 cases of AIN in the series were confirmed by biopsies.

Concomitant medications such as erythromycin in case #1 and amiloride-hydrochlorothiazide in case #2, might have contributed to the first occurrence of AIN in both cases. However, in both cases, symptoms of AIN recurred while patients were receiving omeprazole as monotherapy. Renal biopsy was repeated in case #1 confirming the diagnosis and, therefore, strongly suggesting a temporal association between the event and omeprazole.

Of note, the patient in case #3 was receiving an array of medications in which ampicillin and gentamicin could possibly be associated with AIN. In addition, the patient's serum creatinine levels indicated a slowly increasing trend before starting omeprazole. Although the reporting physician felt that the interstitial nephritis was possibly due to omeprazole, the role of omeprazole in this case needs to be further investigated when additional follow-up information is available.

Conclusion:

This MAR document presents 4 cases of AIN associated with omeprazole from the FDA SRS. Although the etiology of AIN in these cases is unknown, renal function returned to normal after omeprazole was discontinued in 3 cases. AIN recurred upon rechallenge in 2 cases (#1 and #2) which were also published in the literature.

[/S/]
Evelyn Reaud Farinas, R.Ph.

Concurrences:

[/S/]
Min Chen, R.Ph., M.S.
Acting Group Leader

[/S/]
David Barash, R.Ph.
Acting Chief

APPEARS THIS WAY
ON ORIGINAL

CC:
HFD-180/ Gallo-Torres
HFD-730/Johnson
HFD-733/Baum/Freiman/Epi file
HFD-735/Barash/Chen/Farinas/MAR File/Chron
ERF: Disc info

Table 1 - Case #1

Control # Year Type Location	Age/Sex Dose Time to Onset	Concom. Drugs	Reactions Outcome Dec/Rec	Laboratory Values
N121224 1993 15-day Denmark (Literature)*	86/F 40 mg 2 months?/ 9 days	Erythromycin/ None	AIN Hosp. Pos./Pos.	1989 serum cr: normal - pretreatment 858 umol/L - 2 months into treatment 1992 serum cr: 810 umol/L 396 umol/L - 3 months later (Note: normal = <120umol/ L)

This 86 year-old female patient with allergies to amiloride-hydrochlorothiazide, phenylbutazone, and penicillin, and a history of sarcoidosis, was placed on therapy with omeprazole 40 mg daily in 1989 to treat worsening esophagitis. Pretreatment serum creatinine was normal. Prior therapy included ranitidine and cimetidine. Concomitant therapy included erythromycin to treat suspected pneumonia. Two months later the patient experienced renal failure and was hospitalized. Laboratory evaluation revealed a maximum serum creatinine level of 858 umol/L (normal <120). A renal biopsy revealed "interstitial inflammation, with plasma cells, lymphocytes and eosinophil, and patchy tubulitis but no effect on glomeruli. Therapy with omeprazole and erythromycin was discontinued. The patient was treated with diuretics and subsequently regained normal renal function. At this time, erythromycin was suspected of being the drug causing the renal failure.

In 1992, therapy with omeprazole was re-initiated with surveillance of renal function to treat a peptic stricture of the esophagus. Within a week the patient developed high temperature, rash, eosinophilia, and diminishing renal function. The patient did not receive any other drugs, and omeprazole was withdrawn after 9 days. The diagnosis of interstitial nephritis was confirmed by renal biopsy. The renal failure progressed to anuria, and necessitated hemodialysis for a week. Renal function remained severely affected, and after 3 months serum creatinine had declined from 810 to 396 umol/L.

* Christensen, P.B., Albertsen, K.E.P. & Jensen, P. Renal failure after omeprazole. The Lancet. 341: Jan. 1993.

Table 2 - Case #2

Control # Year Type Location	Age/Sex Dose Time to Onset	Concom. Drugs	Reactions Outcome Dec./Rec.	Laboratory Values				
					Before therapy:	At 6 months of therapy:	At 5 weeks p. therapy:	Rechall. p. 2 doses:
#801213 1991 15-day USA (Literature)*	74/F 40 mg/d 6 months	Amiloride Hydrochoro-thiazide (for several years)	Acute renal failure AIN Hosp. Pos./Pos.	BUN:	19 mg/dL	84 mg/dL	16 mg/dL	17 mg/dL
				S cr:	1.2 mg/dL	7.2 mg/dL	1.5 mg/dL	2.2 mg/dL

One year prior to admission, this patient was diagnosed with reflux esophagitis. She was treated initially with famotidine 20 mg/d, but developed recurrent esophageal ulceration with stricture. Six months prior to admission, she was treated with omeprazole 20 mg/d, then 40 mg/d, and after 3 months, the dose was decreased to 20 mg/d because she responded well. Her BUN and creatinine prior to omeprazole therapy were 19 mg/dL and 1.2mg/dL respectively.

This patient was admitted following 2 weeks of generalized malaise, fatigue and anorexia. Five days prior to admission, she discontinued amiloride and hydrochlorothiazide without any relief of symptoms. Routine blood tests showed a blood urea nitrogen (BUN) level of 84 mg/dL and a creatinine level of 7.2 mg/dL. Urinalysis revealed 35 white blood cells per high-power field without renal tubular epithelial cells or red blood cells on microscopic examination. A Wright's stain of urine sediment revealed 6% eosinophil. The patient was diagnosed as having drug-induced acute interstitial nephritis. Upon discontinuation of all the medications her eosinophiluria and orthostatic changes resolved, her appetite improved, and she remained normotensive. BUN and creatinine levels 5 weeks after discharge were 16 mg/dL and 1.5 mg/dL respectively. None of her medications had been restarted in this 5 week period.

At this time, the symptoms of reflux esophagitis returned and omeprazole was re-initiated. After 2 doses, the patient again developed generalized malaise, fatigue, and anorexia. Laboratory values were recorded as follows: BUN (17 mg/dL), creatinine (2.2mg d/L), and pyuria with 16% eosinophil by Wright's stain. Omeprazole was discontinued, and her symptoms resolved rapidly. Renal function improved, with a BUN of 15 mg/dL and a creatinine of 1.6 mg/dL one week after discontinuation of omeprazole. A renal biopsy was deemed unnecessary in light of the rapidly improving clinical picture.

* Ruffenach, S.J., Siskind, M.S. & Lien, Y.H. Acute interstitial nephritis due to omeprazole. The American Journal of Medicine 93: Oct. 1992.

Table 3 - Case #3

Control # Year Type Location	Age/Sex Dose Time to Onset	Concom. Drugs	Reactions Outcome Dec./Rec.	Laboratory Values
651003 1990 15-day USA	62/F 40 mg/d 10 days	Bumex Digoxin Flagyl Ventolin Metolazone Fortaz Carafate Ampicillin Gentamicin	AIN Hosp. Pos./Unk	Serum Creatinine: 1.6 ..... — 1.9 ..... — 2.3 ..... — 2.7 ..... — 3.1 ..... — 3.7 ..... — 5.4 ..... — 6.7 ..... — 7.8 ..... — 7.7 ..... — 6.9 ..... — 2.2 ..... —

This patient with renal dysfunction and post aortic and mitral valve repair was hospitalized in ——— for a hip fracture. On ——— she experienced "coffee ground" vomiting and was started on omeprazole therapy (40 mg/d). On the same day Capoten and Zantac were discontinued. Her other medications were discontinued as follows: Flagyl and Fortaz on —, Digoxin on —. Carafate and Metolazone on — and Ventolin on — Serum creatinine was 1.6 on — prior to omeprazole therapy. However, creatinine values began a steady increase as shown by the following results:

1.6 ..... —	5.4 ..... —
1.9 ..... —	6.7 ..... —
2.3 ..... —	7.8 ..... —
2.7 ..... —	7.7 ..... —
3.1 ..... —	6.9 ..... —
3.7 ..... —	2.2 ..... —

On ——— a renal biopsy showed acute interstitial nephritis. At this time, omeprazole was also discontinued. Serum creatinine values began a slow decrease, reaching 2.3 on ——— The reporting physician felt that the interstitial nephritis was possibly due to omeprazole. Follow-up information has been requested.

Table 4 - Case #4

Control # Year Type Location	Age/Sex Dose Time to Onset	Concom. Drugs	Reactions Outcome Dec./Rec.	Laboratory Values
762167 1991 15-day California	69/M 20 mg 13 days	Isordil Metoprolol	Interstitial nephritis Not reported Unknown/Unknown	None reported

"A physician reported that a 69-year old male who was hospitalized for a myocardial infarction and was being treated with streptokinase complicated by a gastrointestinal hemorrhage was found to have ulcerative esophagitis by endoscopy." He was placed on therapy with omeprazole 20 mg daily . Subsequently the patient developed interstitial nephritis. No further details were provided. Follow-up requests did not contribute additional information.

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Pusey, C.D., Saltissi, D., Bloodworth, L., Rainford, D.J. & Christie, J.L. Drug associated acute interstitial nephritis: clinical and pathological features and the response to high dose steroid therapy. Q.J. Med 1983: 52: 194-211.

Ruffenach, S.J., Siskind, J.S. & Lien, Y H. Acute interstitial nephritis due to omeprazole. The American Journal of Medicine. Vol. 93. Oct. 1992. pp 472-3.

APPENDIX ONE
DRUGS ASSOCIATED WITH ACUTE INTERSTITIAL NEPHRITIS*

B-Lactam Antibiotics
- Methicillin
- Penicillin
- Ampicillin
- Flucloxacil
- Oxacillin
- Nafcillin
- Carbenicillin
- Mezlocillin
- Cephalothin
- Cephalexin
- Cephradine
- Cephalorodidin
- Cefotaxime
- Cefoxitin
- Cefaclor

Other Antibiotics
- Sulfonamides
- Trimethoprim-sulfamethoxazole
- Rifampin
- Polymyxin sulfate
- Ethambutol
- Vancomycin
- Chloramphenicol
- Gentamicin (?)
- Isoniazid (?)
- Minocycline
- Para-aminosalicylic acid
- Ciprofloxacin
- Norfloxacin
- Piromidic acid
- Erythromycin
- Spiramycin

Diuretics
- Thiazides
- Furosemide
- Chlorthalidone
- Ticrynafen
- Triamterene

Nonsteroidal Anti-inflammatory Drugs
- Fenoprofen
- Indomethacin
- Naproxen
- Ibuprofen
- Benoxaprofen
- Phenazone
- Mefenamic acid
- Tolmetin
- Diflunisal
- Zomepirac
- Piroxicam
- Diclofenac
- Ketoprofen
- Suprofen

Other Drugs
- Phenindione
- Glafenin
- Diphenylhydantoin
- Cimetidine
- Sulfinpyrazone
- Allopurinol
- Aspirin
- Carbamazepine
- Clofibrate
- Azathioprine
- Phenylpropanolamine
- Aldomet
- Phenobarbital
- Leukocyte A Interferon
- Floctafenine
- Haldol
- Coumadin
- Tofranil
- Diazepam
- Sodium valproate
- Chlorprothixene
- Captopril
- Propranolol
- Amphetamines
- Doxepin
- Quinine

* From The Principles and Practice of Nephrology (p.349) by H. R. Jacobson, G.E. Striker and S. O. Klahr, 1990, Philadelphia: B.C. Decker, Inc.

Attachment L

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: FEB 14 1994

FROM: Evelyn Farinas, RPh.
Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735

THROUGH: Sandra Kweder, M.D., Acting Director [/S/]
Division of Epidemiology and Surveillance, HFD-730

TO: Stephen Fredd, M.D.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Monitored Adverse Reaction (MAR) Report:
Drug: Omeprazole (Prilosec®)
Reaction: Hyponatremia

Introduction:

Recent receipt of case reports in the FDA Spontaneous Reporting System [SRS] where hyponatremia and/or the syndrome of inappropriate anti-diuretic hormone [SIADH] were reported in association with the use of omeprazole led to this review.

Prilosec® (omeprazole), manufactured by Merck, Sharp & Dohme, was first approved on September 14, 1989 as a 20 mg delayed release capsule. The name was changed in July, 1990 from Losec to Prilosec. Omeprazole is indicated for the short-term treatment of active duodenal ulcer, severe erosive esophagitis, poorly responsive gastroesophageal reflux disease (GERD), and for the long term treatment of pathological hypersecretory conditions (Zollinger-Ellison syndrome, multiple endocrine adenomas and systemic mastocytosis).

Unlike other H2 antagonists which are reversible competitive blockers of histamine at the H2 receptors, omeprazole suppresses the H+/K+ ATPase enzyme system at the secretory surface of the gastric parietal cell, thus blocking the final step of gastric acid production. This effect is dose related and inhibits both basal and stimulated acid secretion irrespective of the stimulus. Onset of the antisecretory effect occurs within one hour, with

the maximum effect occurring within two hours. However, the antisecretory effect of omeprazole lasts far longer due to its strong binding to the H+/K+ ATPase enzyme. Inhibition of secretion is 50% of maximum at 24 hours, and the duration of inhibition lasts up to 72 hours. When the drug is discontinued, the secretory activity returns gradually over 3 to 5 days.

Daily dosage varies according to the condition being treated. Doses of 20 mg daily for 4 to 8 weeks are recommended for the treatment of active duodenal ulcer and GERD. Adult doses for patients having hypersecretory conditions vary according to the individual needs. The recommended adult dose is 60 mg daily, but doses as high as 120 mg three times a day have been administered.

Background:

Osmoreceptors and baroreceptors are sensitive to changes in sodium concentration and volume of extracellular fluids. Approximately, a 2% change in osmolality or a 7-10% change in extracellular fluid volume will trigger the production of ADH from the posterior pituitary. ADH will act on the collecting tubules to increase reabsorption of sodium, leading to an increasingly concentrated urine and an expansion in the extracellular volume.

Hyponatremia may be the result of many factors. It is seen in certain chronic diseases (eg. congestive heart failure, cirrhosis, nephrotic syndrome, etc.) as well as in temporary conditions (eg. vomiting, diarrhea, blood loss, burns, etc). The hyponatremia is associated with a dilutional effect in the former and with sodium loss in the latter. Other causes for hyponatremia include medications, pain, trauma, neoplasms, glucocorticoid deficiency, and SIADH.

In SIADH increased secretion of ADH goes on despite increased extracellular volume. SIADH has been associated with some CNS conditions such as meningitis, stroke and encephalitis; certain respiratory disorders, such as asthma and COPD; and with porphyria and myxedema. Increased basal levels of ADH are also seen in the elderly. It has been suggested that in the elderly, the secretion of ADH can not be stopped completely or that there is a down regulation in the osmoreceptors sensitivity (Davis, 1987).

Adverse Reaction Labelling:

Under the "metabolic/nutritional" and "urogenital" subheadings, the labeling mentions hypoglycemia, weight gain, urinary tract infection, microscopic pyuria, urinary frequency, elevated serum creatinine, proteinuria, hematuria, glycosuria, testicular pain and gynecomastia. Hyponatremia is not listed as a possible adverse event.

Selection of Cases:

We searched the FDA SRS under the mid-level code METSIADH, which includes the following individual COSTART terms: ADH INAPROP, DIABETES INSIPID, HYPONATREM, POLYURIA, THIRST and WATER INTOX. This search identified 19 unduplicated potential cases of hyponatremia and/or SIADH where omeprazole was listed as the suspect drug. Another search under the individual COSTART terms ELECTROLYTE IMBALANCE AND ELECTROLYTE ABNORM captured 1 additional case associating the use of omeprazole with electrolyte abnormalities. Accordingly a total of 20 cases were selected for review.

Thirteen of the 20 case reports were excluded from further review because: the cases did not identify hyponatremia or SIADH as an adverse event (4), the cases clearly identified extra renal sources of sodium loss such as vomiting or dehydration (2), concomitant therapy with drugs (thiazide diuretics or Lozol) or presence of disease (lung cancer or hypopituitarism) which are associated with hyponatremia or SIADH (4), scant information provided (1) and poor temporal association (2). In 1 of these last 2 cases, the 91-year old patient experienced fluctuations in sodium values over the 5 months of omeprazole therapy. In this case, sodium values at the onset of therapy were 138, then dropped to 122, and returned to normal 1 month following discontinuation of omeprazole. Although " a diagnosis of SIADH possibly induced by omeprazole" was made, the case was excluded because follow up information indicated that sodium values also increased to normal while the patient was still receiving omeprazole therapy.

Thus a total of 7 unduplicated cases reporting a drop in serum sodium levels and/or SIADH are presented. Sanitized copies of these 7 cases are also attached.

Demographics:

Age:	49-69 (2), 70-91 (5)
Sex:	Male (4), Female (3)
Daily Dose:	20 mg (4), 40 mg (2), Not stated (1)
Outcome:	Hospitalized (6), Life-threatening (1)
Onset:	2-11 days (4), 2 months (1), 5 months (1), Not stated (1)
Location:	Domestic (3), Foreign (4)
Report type:	15-day (5), Literature (2)
Year:	1990 (1), 1991 (2), 1992 (2), 1993 (2)

Summary of the cases:

A total of 7 cases reporting the development of hyponatremia while on omeprazole therapy are presented in table form. In 2 of these cases the reporting physicians also indicated the development of SIADH. In 4 cases onset of symptoms appeared within 2 weeks of starting omeprazole therapy. In 6 cases sodium values increased after discontinuation of omeprazole.

Case # Control # Type Year Location	Age/Sex Onset Dose/d	Sodium level in mmol/L before tx/ during tx/ after tx	Out. Dech. Rech.	Concom. Drugs	Comments
#1 854036 Liter. 1992 France	70/M 3 d 40 mg	135/ 118-115/ 136	Hosp. (+) NA	Folic Acid Iron Vit. B1 Vit. B6 (Dates not indicated)	A 70-year old alcoholic man was hospitalized for anemia associated with esophagitis and GI ulcerations. He was taking folic acid, iron and vitamin B1 and B6 supplements. He was given glucose solution, drank 1 liter of water daily and ate normally. On day 9 of hospitalization, treatment with 20 mg of omeprazole q 12 hours began following endoscopy. On day 12, 3 days after initiating omeprazole, the patient became mildly comatose, and the serum sodium level decreased to 118 mmol/L from a previous level of 135 mmol/L. Saline as a 9% solution and absolute water restriction were initiated. On day 13, sodium value was 115 mmol/L and urine volume was 1000-1500 cc/24 hr. On day 15, the patient developed pneumopathy with a fever of 38.4 degrees C. Amoxicillin treatment began, with resolution of the pneumopathy in 48 hours. Sodium level remained at 115 mmol/L. Omeprazole was discontinued. ADH level was 3 pmol/L with osmolarity of plasma at 250 mosm/L and that of urine at 300 mosm/L. Based on these tests a diagnosis of SIADH was made. The patient was treated with demeclocycline at 750 mg/24 hours, from day 14-17. Sodium level started going up (136 mmol/L on day 19). The patient returned to normal consciousness and sodium levels remained normal over the next month. Other tests (CSF, HIV, Lyme disease, Thyroid hormone, Cortisol, Calcium, porphyria) as well as alcohol or medication intake were negative.
#2 937781 Liter. 1993 France	84/F 11 d 20 mg	Normal/ 108-106/ 130	"Life Threatening" (+) NA	Digoxin Aldactazide Maalox (Dates not indicated)	An 84-year old woman with cardiomegaly, mitral valve disorder and arrhythmia, had been receiving treatment with digoxin, HCTZ with spironolactone, and aspirin every other day, when omeprazole treatment (20 mg daily) began for treatment of an uncomplicated antral ulcer. At this time blood electrolyte levels were normal. Aspirin was discontinued. Eleven days later, the patient developed asthenia with no evidence of edema, fever or hemodynamic instability. Serum sodium dropped to 106 mmol/L. The ratio of sodium to potassium in urine remained stable (54/41 mmol/l Omeprazole was discontinued. Eight days later, serum sodium was up to 130 mmol/L. No further electrolyte imbalance was seen.

Case # Countr # Type Year Location	Age/Sex Onset Dose/d	Sodium level in mmol/L before tx/ during tx/ after tx	Out. Dech. Rech.	Concom. Drugs	Comments
#3 824223 15-day 1992 USA	71/F 2 d 20 mg	144/ 110-107/ Normal	Hosp. (+) NA	Dyazide Elavil Cardiazem SR Cardura Eagic Feldene Zantac Nitrostat Percocet IV fluids (Therapy of several months duration)	This 71-year old female was admitted with complaints of severe pain in the right side of the abdomen accompanied by nausea. She denied vomiting, irregular bowel movements and bloody or black stools. Past medical history consists of frontal headaches, hypertension, depression, chest pain, dizziness, back pain, knee replacement, arthritis pain and leg edema. In the past, she had taken Zantac to relieve pain in the stomach area. On the day of admission, Zantac was stopped and omeprazole therapy, 20 mg daily, was started. All her previous blood pressure medications were continued (Cardura, Dyazide and Cardizem SR). Two days later, the patient became confused, restless, agitated, and disoriented. At the time, acute psychosis, withdrawal syndrome or reaction to some medication were being considered as causes for these symptoms. Laboratory findings indicated a sodium level of 110, and later that day 107, down from 144 on day of admission. She was seen by a psychiatrist and a neurologist. A CT scan was normal. The patient was treated with 3% sodium chloride with 30 meq of potassium, and the omeprazole and Dyazide were discontinued. Three days later electrolytes had returned to normal. Follow up information from the physician indicated that the diagnosis of SIADH was established by urinary and serum osmolality (583 and 227 respectively, normal u.o. 300-900 and normal s. o. 280-301), electrolytes, mental status changes compatible with SIADH and by the patient's recovery upon discontinuation of the drug. The reporting physician did not rechallenge this patient with omeprazole.
#4 724548 15-day 1991 USA	61/M Not stated 40 mg	126-130/ 112/ Not stated	Hosp. (+), NA	Pericolace Lanoxin Vitamins Tobradex Cyclogil Iron	A 61-year old male with a history of hyponatremia and peripheral neuropathy of unknown etiology was placed on therapy with omeprazole for treatment of erosive esophagitis. While on therapy the patient's serum sodium dropped to 112. The patient was hospitalized and treated with fluid restriction and demeclocycline. Attempts to contact the reporter for additional information have not been successful.
#5 766317 15-day 1991 USA	77/M 7 d 20 mg	Not stated/ 123/ Returning to normal	Hosp. (+) NA	Verapamil Tenormin	One week after initiation of omeprazole this 77-year old man became confused. He was hospitalized. Lab values indicated a sodium level of 123 and a decreased hemoglobin. A diagnosis of pancytopenia was made. Therapy with omeprazole was discontinued and the patient was treated with IV sodium. At the time of the report laboratory values were returning to normal.

Case # Control # Type Year Location	Age/Sex Onset Dose/d	Sodium level in mmol/L before tx/ during tx/ after tx	Out. Dech. Rech.	Concom. Drugs	Comments
#6 937833 15-day 1993 USA	83/M 2 mths? 20 mg	Not stated/ 115/ 127	Hosp. (+) NA	Digoxin Aspirin Thioridazine Cataridol	An 83-year old male with cardiomegaly and a history of CVA with left hemiplegia and tachyrhythmia was placed on therapy with omeprazole 20 mg daily to treat esophagitis Grade III. Approximately, 2 months later the patient was hospitalized for chronic thoraco-abdominal pain. Endoscopy revealed mild hiatal hernia, probable esophageal candidiasis and Grade II esophagitis. On the day of admission sodium values were recorded as 115. Therapy with omeprazole was increased to 40 mg daily. Treatment with physiological saline did not increase the sodium level which led to a suspicion that a drug effect had caused Schwartz-Barter syndrome. Therapy with omeprazole was discontinued and treatment with demeclocycline was started. Sodium values increased to 127. Follow up information indicated that the patient was subsequently treated with ranitidine.
#7 663669 15-day 1990 France	49/NS 5 months? NS	Not stated/116/130-128	Hosp. (+) NA	Creon Vitamin B1 Vitamin B6 Nicobion Insulin	A 49-year old patient with pancreatitis who was being treated with pancreatic enzymes and vitamins was placed on therapy with omeprazole for treatment of anastomotic gastric ulcer. Approximately 5 months later the patient presented with generalized epileptic crisis and was hospitalized. Serum sodium was 116. Tomography revealed cortico/subcortical atropy. The following day urine sodium was 90 and omeprazole was discontinued. The patient was treated with physiologic saline and clonazepam. Repeat laboratory evaluation revealed serum sodium of 130 Urine sodium increased to 107. After discontinuation of saline therapy, serum sodium decreased to 128. The patient continued under treatment at the time of the report.

Discussion:

Reporters in all 7 cases identified a decreased sodium level during the administration of omeprazole in adult patients whose median age is 70. In 6 of the 7 cases, an increase in the patient's sodium values followed the discontinuation of omeprazole. In the 4 cases indicating sodium values prior to therapy, the sodium drop was 10% or more of the pre-therapy values. Six of the cases indicated that the electrolyte imbalance was treated with sodium and/or demeclocycline.

In the 2 cases where the reporting physicians indicated SIADH in addition to hyponatremia, diagnosis was based on laboratory values. In case #1, ADH values above normal were recorded during omeprazole therapy coincidental with low sodium levels. In case #3, the physician indicated in follow up that the diagnosis of SIADH was "definitely established" by urinary and sodium osmolality as well as electrolytes. In addition, mental status changes (light coma in case #1 and confusion, agitation and restlessness in case #3) were compatible with a diagnosis of SIADH. Further, in case #3 the patient was examined by a psychiatrist who indicated that there was an organic cause for the existing abnormal mental state.

Literature reports have indicated disturbances in water and electrolyte regulation in the elderly together with increased levels of ADH, suggesting altered tubule permeability or decreased susceptibility to ADH.[1,2] The omeprazole labeling identifies adverse events (hematuria, pyuria and glycosuria) which may be associated with altered tubule permeability. Thus the effects of omeprazole in the kidneys in a population already identified at risk should be monitored more carefully.

Conclusion:

We present 7 cases of adult patients where serum sodium decreased after the initiation of omeprazole therapy and increased or returned to normal once omeprazole was discontinued. In 2 cases a diagnosis of SIADH was made in addition to the hyponatremia. We present these cases to convey information presently available in the FDA SRS.

[/S/]

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2. Davis PJ, Davis FB. Water excretion in the elderly. Endocrinology and Metabolism Clincis. 1987;16(4): 867-875.

Attachment M

CONTAINS NON TRADE SECRET DATA
FOR FDA INTERNAL USE ONLY
DO NOT RELEASE OUTSIDE FDA

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: DEC 31 1997

FROM: Carol Pamer, R.Ph., Postmarketing Safety Evaluator
Reports Evaluation Branch, HFD-735 [ISI] for

THROUGH: Robert O'Neill, Ph.D., Acting Director
Division of Pharmacovigilence and Epidemiology, HFD-730 [ISI] 23 Dec 97

TO: Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Monitored Adverse Reaction Report: Omeprazole (Prilosec®)
Anaphylaxis and Anaphylactoid-type Reactions

Background and Introduction

In response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), the FDA Spontaneous Reporting System was searched for reports of possible anaphylactic and anaphylactoid-type reactions with omeprazole, a proton-pump inhibitor. Omeprazole is a substituted benzimidazole that inhibits gastric acid secretion. Prilosec® Delayed-Release 20mg capsules (Astra Merck, U.S.) were approved for use in the U.S. on September 14, 1989. The 10mg capsules were approved on October 5, 1995. Prilosec® capsules are indicated as treatment for the following conditions: active duodenal ulcer (short-term), active benign gastric ulcer (short-term), heartburn and other symptoms associated with GERD, erosive esophagitis (short-term, endoscopy-diagnosed and maintenance of healing), and pathological hypersecretory conditions such as Zollinger-Ellison syndrome, multiple endocrine adenomas, and systemic mastocytosis (long-term). Prilosec® in combination with clarithromycin is also indicated for the treatment of patients with *H.pylori* infection and active duodenal ulcer to eradicate *H.pylori*.

In the current product labeling for Prilosec® (omeprazole) delayed-release capsules under "ADVERSE REACTIONS", the possibly-related terms "urticaria" and "angioedema" are labeled as reported in <1% of omeprazole-treated patients in domestic and/or international trials or since the drug was marketed, with the relationship to Prilosec® unclear. Anaphylaxis, anaphylactoid-type reactions, allergic reactions or related syndromes do not specifically appear in the labeling.

Medical Literature

The medical literature was searched for possible literature reports of anaphylaxis, allergic reactions, or anaphylactoid-type reactions with omeprazole using the terms "anaph", "allerg", or "hypersens". Of the 14 total citations retrieved with this search strategy, 2 were determined to be relevant[2,3]. They both were previously submitted by the manufacturer (see Astra Merck 19960700016 and Merck Sharp & Dohme WAES 93070295).

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[1] Date issued September 1997.
[2] Ottervanger JP, Phaff RAS, Vermeulen EGJ, Stricker BHC. Anaphylaxis to omeprazole. J Allergy Clin Immunol 1996; 97(6):1413-1414.
[3] Bowlby HA, Dickens GR. Angioedema and urticaria associated with omeprazole confirmed by drug rechallenge. Pharmacotherapy 1993; 14(1):119-22.

Selection of Cases

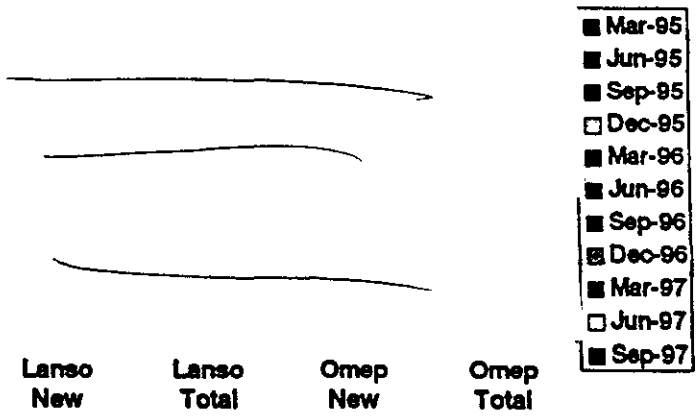
The FDA Spontaneous Reporting System (SRS) database was searched for reports of anaphylactoid-type events occurring during the use of omeprazole using the DES midlevel term "Anaphylactoid Reactions" which retrieves all reports where the COSTART ANAPHYL appears or where terms from 2 of the 3 following body systems are present. Cutaneous terms include ANGIOEDEMA, URTICARIA. Cardiovascular terms include HYPOTENS, SHOCK. Respiratory terms include APNEA, ASTHMA, DYSPNEA, EDEMA LARYNX, HYPOVENTIL, LARYNGISMUS, RESPIRAT DIS, STRIDOR.

As of 10/10/97, there were 35 reports in the SRS for omeprazole which met these criteria. All reports were retrieved and reviewed, for a total of 34 unduplicated cases. Seven (7) cases were excluded for the following reasons: confounded by cephalosporin or penicillin product (n=3), confounded by codeine allergy and meperidine use (n=1); several suspect drugs with omeprazole continued (n=1); and symptoms did not appear allergic, anaphylactic or anaphylactoid-related (n=2). Twenty seven (27) cases remained.

Drug Utilization Data (Note: Trade secret data. For FDA internal use only.)

Data were obtained from the National Prescription Audit Plus (NPA Plus), which is a measure of new and refilled prescriptions that move out of over——— retail pharmacies into the hands of consumers via formal prescriptions. Numbers represent extrapolated number of prescriptions dispensed per specified quarter year. A search of the database as of October 1997 resulted in the following data:

IMS Use Data (Rx in ——)



Summary of cases

his series was comprised of 27 cases, which are listed in Attachment #1. Demographics of these 27 cases are presented in Table 1. Selected cases are also described in the latter portion of this section.

Table 1: DEMOGRAPHICS*

SEX (n=25)	Female 14; Male 11; Not stated 2
AGE (n=23)	Mean, 47 y.o. Median, 48 y.o. Range, 20 to 73 y.o.
DAILY DOSAGE (n=20)	20 mg
TIME TO ONSET (n=22)	Mean, 2.7 days Median, 1 day/dose Range, 1 day/dose (n=13) 2-7 days (n=7) 9 days (n=1) 11 days (n=1)
OUTCOME	Hospitalized/ER 21; Life-threatening 2; Deaths 0; N/A or not specified 4
DECHALLENGE	Positive 22; Negative 0; N/A or not specified 5
RECHALLENGE	Positive 1; Negative 1"; N/A or not specified 25
SOURCE	Domestic 16; Foreign 11

*N=27, unless otherwise stated.

"One literature case was received in which the patient experienced a negative rechallenge when enteric-coated beads were administered without the gelatin capsule.

Twenty-three (23) cases reported a serious outcome, although none were fatal. Sixteen (16) were domestic, 11 foreign. In more than half of the cases where that information was reported, the adverse events began following the first dose of omeprazole (n=13 of 22 cases); 20 of 22 cases had a reported time to onset of symptoms of 7 days or less. Of those where it was specifically stated, 6 had taken previous courses of omeprazole therapy and one used omeprazole "chronically". In one report, it appeared that the patient had not taken omeprazole previously. Of the 27 cases, 9 patients had a definite history of previous allergies and/or asthma, one of which was patient-reported pruritus and a second case of urticaria, both associated with previous use of omeprazole. Six (6) cases clearly stated that the patient had no history of allergies.

One (1) case (FDA 1422346) specifically reported that omeprazole was a "new" therapy, which raises the possibility of an *anaphylactoid-type reaction*. This patient experienced urticaria, hypotension, dizziness, and blurred vision after 1 dose of omeprazole. He was hospitalized for the events. The report also specifically stated that the patient had no history of allergies.

Seven (7) cases specifically reported previous courses of therapy with omeprazole, one as "chronically". These cases may represent true *anaphylactic or hypersensitivity-type reactions*. Time to onset of symptoms was 1 day (n=3), 2 days (n=1), 3 days (n=1), 11 days (n=1), and unknown (n=1).

Previous use of omeprazole or other proton pump inhibitors is not specifically known or stated in the remaining 19 cases. In the 15 of 19 cases where that information was provided, the time to onset of symptoms was 1 dose (n=9), 2 to 7 days (n=5), and 9 days (n=1). Specific inquiry regarding previous exposure to omeprazole would be necessary to be able to categorize these reactions as true anaphylactic reactions or anaphylactoid-type reactions.

none of the cases specifically reported the use of lansoprazole before or after the event(s). Although lansoprazole has been available in other countries for a number of years, lansoprazole has only been approved in the U.S. for about 2.5 years. Ten (10) cases in this series for omeprazole occurred after 1994, 7 of which were foreign. It also is not known if lansoprazole was prescribed at a later date, beyond the time when follow-up would have been conducted by the manufacturer.

SELECTED CASES:

1. 19940900002: a 56 y.o. male with hypertension, myocardial ischemia was placed on therapy with omeprazole for recurrent duodenal ulcer. Other medications included isosorbide mononitrate and nifedipine. On the third day of this course of omeprazole oral therapy, he experienced life-threatening anaphylactic shock one hour after his dose. The reaction lasted 60 to 90 minutes and consisted of generalized urticaria, dizziness, loss of consciousness, thoracic pain and feeling of thoracic pressure. He was treated for the shock and recovered. He had no history of allergies and *had taken omeprazole before without incident*. Intradermic *skin test with dilution of omeprazole was positive*; tests performed in 6 control subjects were negative. RAST test indicated no IgE antibodies to omeprazole.

2. 19960700016: Literature report (Ottervanger et al) of 47 y.o. male was placed on omeprazole 20mg daily for treatment of burning gastric pain. He was not taking any other medications. Six weeks later, he was admitted to a hospital with nausea, vomiting and abdominal pain: at an unspecified point in time, he had *previously discontinued omeprazole due to urticaria*. Lab results and ECG were normal at time of admission. The second day of hospitalization he received *omeprazole 40mg intravenously*. Within a few minutes of administration, he experienced urticaria, angioedema, severe hypotension, unconsciousness followed by asystole. He was resuscitated and he recovered after 1 day. Several weeks later, a *skin test with omeprazole (prick test) resulted in wheal and erythema* at the test site within 10 minutes; tests performed in control subjects were negative.

3. 93070295: Literature report (Bowlby and Dickens) of a 34 y.o. female who had been hospitalized for cellulitis likely due to IV drug abuse and was receiving intravenous famotidine, vancomycin and gentamicin. Endoscopy had shown ulcerative, erosive esophagitis as well as gastric and duodenal ulcers. Day 4 of hospitalization she was placed on omeprazole 20mg oral. On Day 5 of hospitalization she developed sudden SOB, cough, wheezing, CXR which showed right pleural effusion following *Dose 2 of omeprazole* and vancomycin. *Eosinophil count was 11%*. She was treated with inhaled albuterol and heparin. Pulmonary embolism and DVT were ruled out and heparin discontinued. She remained stable during Day 6 of hospitalization, with complaints of dry throat, hoarseness, nonproductive cough. However in the morning of hospital Day 7 following *omeprazole Dose 4*, cimetidine, albuterol, and intravenous vancomycin and gentamicin, she developed *facial angioedema, increasing SOB* which was treated with diphenhydramine. The next day, she was *given omeprazole without the gelatin capsule*. An hour later, she developed generalized urticaria and pruritus. *Omeprazole was discontinued and no further reactions occurred.*

4. 1422346: a 73 y.o. male was prescribed omeprazole 20mg for epigastric pain. *2 hours after initial dose* he developed generalized urticaria, followed by dizziness, blurred vision, and hypotension. He was treated and released at an emergency room with diphenhydramine, epinephrine, methylprednisolone, cimetidine, potassium and antacid. *Prilosec was reported as the only new drug* prescribed and used on a "prn" basis. *He had no history of allergies*. Home meds included niacin, Hytrin, and Prinivil.

5. WAES 91080581: *Literature report*[4] of a 44 y.o. male with a *history of allergy to azo-dyes and urticaria with pseudoephedrine linctus* was placed on omeprazole 20mg for treatment of Barrett's esophagus. *Two hours after the first dose*, he developed urticaria, facial angioedema, and bronchospasm. He was hospitalized and recovered after treatment with intravenous corticosteroid. *Two days later, he took a second dose* of omeprazole and the *symptoms recurred*. Omeprazole was discontinued. He was treated with cimetidine for 4 weeks with no episodes of urticaria or angioedema. *Additional single doses of omeprazole given at 2-week intervals each resulted in urticaria and*

[4] Haeney MR. Angio-oedema and urticaria associated with omeprazole (letter). BMJ 1992 Oct 10; 305:870.

angioedema within 3 hours. *Subsequently, he was given the enteric coated granules of omeprazole which had been removed from the gelatin capsule and allergic symptoms did not recur.*

Discussion

Currently the U.S. product labeling for Prilosec® (omeprazole) includes only "urticaria" and "angioedema" among those symptoms which could possibly be related to anaphylaxis or anaphylactoid-type reactions. Our analysis of the cases of possible anaphylactic and anaphylactoid-type reactions received through the FDA Spontaneous Reporting System (SRS) for omeprazole indicates that these types of events may be related to the use of omeprazole. The outcome in many of the cases was serious, as would be expected with these conditions. Twenty-one (21) patients required hospitalization or emergency room treatment. Two (2) reporters categorized the events as life-threatening. Due to the nature of the short-term, intermittent treatment of some of the labeled indications for omeprazole, the possibility of previous sensitization to the product is possible in susceptible patients. Some investigation as to the possibility of cross-sensitivity to other proton pump inhibitors should also be considered. Although there were no reports suggestive of this phenomenon in this report, a previous Monitored Adverse Reaction Report for Prevacid® (lansoprazole) included one case where a patient with history of serum sickness and urticaria with omeprazole developed anaphylaxis with lansoprazole (see Attachment #2).

Consideration should be given to include these events in the current U.S. product labeling. Addition of a specific **Postmarketing Reports** section may also be considered, with a suggested introductory paragraph as follows:

> The following events have been identified during post-approval use of omeprazole products in clinical practice. Because they are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. These events have been chosen for inclusion due to a combination of seriousness, frequency of reporting, or potential causal connection to omeprazole:
>
> HYPERSENSITIVITY: In addition to isolated urticaria and angioedema, possible allergic, anaphylactic and anaphylactoid reactions have been reported with omeprazole use.

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Concur:

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ATTA..MENT #1: CASES INCLUDED FOR ANALYSIS (N=27)

Mfr/FDA #	Source	Year	Reaction(s)	Outcome	Tx w/Rx	Sex	Age	Dose (mg)	Onset (days)
)1080581	Foreign	1990	Angioedema, urticaria, bronchospasm	Hosp/ER	Yes	Male	44	20	1
)0030197	U.S.	1990	Anaphylaxis	Hosp/ER	Yes	Female		20	1
)1020212	U.S.	1991	Anaphylactic reaction	Hosp/ER	Yes	Female	48		11
)2090510	U.S.	1992	Allergic reaction: angioedema, urticaria, laryngismus	Hosp/ER	Yes	Female	50	20	1
)3070295	U.S.	1992	Asthma, angioedema, hoarseness, voice changes	Hosp/ER	Yes	Female	34	20	2
)2060297	U.S.	1992	Urticaria, dyspnea, vertigo, rash, pruritus	N/A or unknown		Female	36	20	1
)2040217	U.S.	1992	Anaphylactic reaction	Hosp/ER	Yes	Female			
)2080473	U.S.	1992	Anaphylaxis	Hosp/ER	Yes	Male	42	20	7
)2060750	U.S.	1992	Anaphylactoid reaction, angioedema	N/A or unknown	Yes	Male	69		3
.422346	U.S.	1993	Urticaria, hypotension, dizziness, blurred vision	Hosp/ER	Yes	Male	73	20	1
.9940900002	Foreign	1993	Anaphylactic shock, skin test positive	Life-threatening		Male	56	20	3
)4030450	U.S.	1993	Anaphylactic reaction	N/A or unknown		Male	31		
)3020027	U.S.	1993	Anaphylaxis	N/A or unknown					
1450198	U.S.	1994	Urticaria, angioedema, asthma, tachycardia	Hosp/ER		Female	27	20	
.9950400064	Foreign	1994	Shock, urticaria, erythema, pruritus, LST positive	Hosp/ER	Yes				3
19941200084	U.S.	1994	Anaphylactic reaction	Hosp/ER	Yes	Female	55	20	
19950400087	Foreign	1994	Urticaria, laryngeal edema	Hosp/ER	Yes	Female	48	20	7
19951200097	Foreign	1995	Anaphylactic shock	Hosp/ER	Yes	Male	31	20	1
19951000184	U.S.	1995	Angioedema, tongue & laryngeal edema	Hosp/ER	Yes	Female	66	20	1
19951000166	Foreign	1995	Anaphylactic shock	Hosp/ER	Yes	Female	56	20	1
19951000267	Foreign	1995	Shock, respiratory arrest, seizures	Life-threatening		Male	47	20	1
1603194	U.S.	1995	Angioedema, laryngeal edema	Hosp/ER		Female	57	20	1
1764144	U.S.	1996	Angioedema, SOB, severe rash	Hosp/ER		Female	58		9
19960700016	Foreign	1996	Urticaria w/oral, anaphylaxis w/IV. Skin test positive	Hosp/ER	Yes	Male	47	20	1
19960400015	Foreign	1996	Tongue edema, pruritus, feeling of suffocation	Hosp/ER	Yes	Female	20	20	1
19970400271	Foreign	1997	Anaphylactic shock	Hosp/ER	Yes	Male	51	20	1
19970300182	Foreign	1997	Urticaria, laryngeal edema, pruritus, rash	Hosp/ER		Male	24	20	2

ATTACHMENT #1: CASES INCLUDED FOR ANALYSIS (N=27), contin

Mfr/FDA	D/C+	R/C+	Literature	Hx asthma, allergy[5]	Previous use[2]
91080581	Yes	No	Yes	Yes--azo-dyes	
90080197	Yes				
91020212	Yes			Yes--penicillin	Yes
92090510	Yes			Yes--sulfa, penicillin; asthma	
93070295	Yes	Yes	Yes	No known drug allergies	
92060297	Yes				
92040217					
92080473	Yes			No history of allergies	
92060750	Yes			Rx prednisone (inflammatory bowel)	
1422346	Yes			No history of any allergies.	No
19940900002	Yes			No drug allergy, atopy	Yes
94030450				Yes--OTC Rx, red dye? Anaphylaxis	
93020027					
1450198	Yes			NKA (meds, environ), no hx anaphyl	"Chronically"
19950400064	Yes				
19941200084	Yes			No known allergies	
19950400087	Yes			Yes--penicillin	
19951200097	Yes				Yes
19951000184	Yes			Yes--asthma	
19951000166	Yes				
19951000267	Yes				
1603194					
1764144				Yes--sulfa, codeine, Rx albuterol	
19960700016	Yes		Yes	Yes--urticaria w/omeprazole	Yes
19960400015	Yes				
19970400271	Yes			Yes--pruritus w/omeprazole	Yes
19970300182	Yes				Yes

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[5] Information included when specifically mentioned in text of report. It is not known if patients and reporters were directly queried regarding these items.

ATTACHMENT #2

Monitored Adverse Reaction Report: Lansoprazole (Prevacid®)
Subject: Anaphylaxis and Anaphylactoid-type Reactions
Date: July 11, 1997

6 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Attachment N

CONTAINS BMS TRADE SECRET INFO
FOR FDA [illegible] USE ONLY
DO NOT RELEASE OUTSIDE FDA

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID#

DATE:

FROM: Ann Corken, RPh, MPH, Safety Evaluator
Division of Drug Risk Evaluation II (DDRE II)

THROUGH: Evelyn Rodriguez, M.D., M.P.H., Director
DDRE II, HFD-440

11/22/99

TO: Lilia Talarico, M.D., Director
Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Consult: Determination of the use for omeprazole (Prilosec) in women of childbearing age (15 to 45 years).

EXECUTIVE SUMMARY:

Gastrointestinal and Coagulation Drug Products, HFD-180, requested information on the use for omeprazole (Prilosec) in women of childbearing age (15 to 45 years) as part of an ongoing evaluation of omeprazole's potential for OTC switch. Information from the National Disease and Therapeutic Index (NDTI) and the National Prescription Audit (NPA) databases for combined years 1996, 1997, 1998, and 1999 (through August) were used to calculate the percentage use in women of childbearing age and then the estimated number of prescriptions dispensed.

Information calculated using NDTI data indicated that the percentage use in women of childbearing age for omperazole was ——→note that there is no way of knowing the number of women in this group who were pregnant while receiving omeprazole). The percentage was then combined with the total number of prescriptions dispensed and the total estimated use for combined years 1996, 1997, 1998, and 1999 (through August) in women of childbearing age was ——— prescriptions.

INTRODUCTION:

This memorandum is in response to a consult received from HFD-180 requesting information on the use for omeprazole (Prilosec) in women of childbearing age (15 to 45 years). The information provided is part of the ongoing evaluation of omeprazole's potential for OTC switch.

METHODS:

The following formula was used in performing the calculations shown below:

NDTI drug appearances in specified gender and age group/NDTI drug appearances in all age groups X (NPA total Rx dispensed) = Estimated Rx dispensed in specified gender and age group

NDTI = National Disease and Therapeutic Index
NPA = National Prescription Audit
Rx = prescriptions

NDTI and NPA data were obtained for the years 1996, 1997, 1998, and 1999 (through August).

RESULTS:

Omeprazole (Prilosec)

Females, ages 15 to 45 years:
— of total drug appearances were in females aged 15 to 45 years; the estimated prescription use in females aged 15 to 45 years is ——— for combined years 1996, 1997, 1998, and 1999 (through August).

DISCUSSION/CONCLUSION:

This document describes estimated use of omeprazole in women of childbearing age (15 to 45 years) based on NDTI and NPA databases. NDTI database is a continuing survey designed to provide statistical and demographic information about the patterns and treatment of disease encountered in office-based practice in the U.S. NPA database measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. One limitation of the NDTI database is that it is a sample-based estimate and thus has the potential for a sampling error.

Information calculated using NDTI data indicated that the percentage use in women of childbearing age for omeprazole was — (note that there is no way of knowing the number of women in this group who are pregnant while receiving omeprazole). The percentage was then combined with the total number of prescriptions dispensed and the total estimated use in women of childbearing age for the combined years 1996, 1997, 1998, and 1999 (through August) was ——— prescriptions.

[/S/]
Ann Corken, RPh, MPH

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Watch

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINSTRATION	**OPDRA POSTMARKETING SAFETY REVIEW**	
Lilia Talarico, M.D., Director Division of Gastrointestinal and Coagulation Drug Products HFD-180	**FROM:** Ann Corken, RPh., MPH, Safety Evaluator Division of Drug Risk Evaluation II (DDREII) HFD-440	**OPDRA PID #** D000223 AUG 16 2000
DATE REQUESTED: March 15, 2000 **DATE RECEIVED:**	**REQUESTOR/Phone #:**	
DRUG Est (Trade): cimetidine (Tagamet) famotidine (Pepcid) nizatidine (Axid) rantidine (Zantac)	**NDA/IND # 19-810** (Omeprazole)	**SPONSOR:** Astra-Merck

Executive Summary: The attached printouts (ADRs by preferred term and cases by year and quarter) for cimetidine, famotidine, nizatidine, and ranitidine were prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review the adverse event profile for GI drugs that have been switched from Rx to OTC because the sponsor for omeprazole has submitted an NDA for a change to nonprescription status. Note that these printouts include the U.S. experience only up to March 31, 2000.

Reason for Request/Review: Omeprazole (Prilosec) is indicated to treat duodenal ulcer and gastric ulcer, symptomatic GERD, erosive esophagitis, pathological hypersecretory conditions, and for maintanence of healing of erosive esophagitis. It is marketed by Astra Merck and was approved on September 14, 1989. Division HFD-180 has requested a review of the safety profile of GI drugs that have been switched from Rx to OTC because Astra Merck has petitioned for an Rx to OTC switch for omeprazole.

evant Product Labeling:

Search Date: see above	**Search Type(s):** AERS X Literature Other

Search Results: See attached printouts.

Discussion / Conclusions: The attached printouts (ADRs by preferred term and cases by year and quarter) for cimetidine, famotidine, nizatidine, and ranitidine were prepared in response to a request from Lilia Talarico of HFD-180 dated March 15, 2000 to review the adverse event profile for GI drugs that have been switched from Rx to OTC because the sponsor for omeprazole has submitted an NDA for a change to nonprescription status. Note that these printouts include the U.S. experience only up to March 31, 2000. An assessment of these reports has not been done and some of these numbers may represent duplicate reports. Further, conclusions regarding comparative safety of these drugs cannot be made due to the many factors influencing spontaneous reporting.

Reviewer's Signature / Date: [/S/] 8/15/00 Ann Corken, RPh, MPH	**Team Leader's Signature / Date:** [/S/] 8/15/00 Toni Piazza-Hepp, Pharm.D
Division Director Signature / Date: 8/16/00 [/S/] Deputy Director for Evelyn Rodriguez	**Office Director Signature / Date:**

Attachments:

NDA # 19-810
HFD-180 Division File/Div Dir / MO / SMO / Project Manager
HFD-430/440 DD/TL/SE/Chron/Drug
HFD-400 Honig
Electronic File Name:

Adverse Event Reporting System (AERS)

Standard Report

Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 05/31/2000 - 09:57 am

Search Criteria:

Product Name(s):

- CIMETIDINE (A)
- CIMETIDINE HYDROCHLORIDE (A)
- TAGAMET (CIMETIDINE) (V)
- TAGAMET (T)
- TAGAMET (V)
- TAGAMET (CIMETIDINE) 400 MG (V)
- TAGAMET (CIMETIDINE) HB (V)
- TAGAMET HB (V)
- TAGAMET HB (CIMETIDINE) (V)
- TAGAMET HB 200 (V)
- TAGAMET HB 200 (CIMETIDINE) (V)
- TAGAMET HB 200 MG SMITHKLINE BEECHAM CONSUMER HEALTHCARE (V)
- TAGAMET HB 200MG (V)
- TAGAMET HB SMITHKLINE BEECHAM CONSUMER HEALTHCARE (V)

Manufacturer Type: Sender of ISR

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dverse Ev..t Reporting System (AER

Standard Report

Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 05/31/2000 - 09:57 am

earch Type: CASE
earch for reactions listed: ANY
DA Rcvd. Date: From:
eporter Domestic: YES
eporter First Name:
ull Values for Country
emale:
ge Range: From
edWatch Source Study
edWatch Source Health Professional:
xpedited (15-Day) ISR:
A Summary ISR
clude Deactived ISRs
o -Serious Outcome:
vent End Date:
T(Products Only:

Include Concomitant Products:
ISR/Case #:
FDA Rcvd. Date: To: 03/31/2000
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products
Mfr. Control #:
Sort in Descending Order
Reporter Last Name
Reporter State
Male
Null Gender Value
Age Range: YEAR
MedWatch Source Consumer
Periodic ISR
5 Day ISR
Follow-up
Serious Outcome
Event Start Date:
ReC

on-Excluded Product(s) for Selected Active Ingredient(s):

METIDINE (T)
AGAMET HB (T)
METIDINE (V)
IMETINDENE (V)
CIMETIDINE HCL (T)
TAGAMET HB 200 (T)
CIMETIDINE (CIMETIDINE) TABLET 400 MG (V)
TAGAMET HB (V)
MAALOX FAST BLOCKER (T)
ACINIL (V)
CIMETIDINE TABLETS, 400 MG - GENEVA (V)
TAGAMET (T)
CIMETADINE (V)
CIMETIDINE, GA301 (V)

xcluded Produc(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
4	67	3	3	0	0	0	0	0
Subtotal	67	3	3	0	0	0	0	0
1	171	8	8	0	0	0	0	0
2	51	2	2	0	0	0	0	0
3	110	3	3	0	0	0	0	0
4	42	2	2	0	0	0	0	0
Subtotal	374	15	15	0	0	0	0	0
1	88	13	5	9	0	0	0	0
2	273	10	10	0	0	0	0	0
3	15	1	1	0	0	0	0	0
4	111	9	9	0	0	0	0	0
Subtotal	487	33	25	9	0	0	0	0
1	99	3	2	1	0	0	0	0
2	36	2	2	0	0	0	0	0
3	35	3	3	0	0	0	0	0
4	11	1	1	0	0	0	0	0
Subtotal	181	9	8	1	0	0	0	0
1	51	7	7	0	0	0	0	0
2	167	24	23	1	0	0	0	0
3	245	15	13	2	0	0	0	0
4	245	8	8	0	0	0	0	0
Subtotal	708	54	51	3	0	0	0	0
1	189	17	12	7	0	0	0	0
2	340	55	42	18	0	0	0	0
3	318	46	23	29	0	0	0	0
4	128	31	15	20	0	0	0	0
Subtotal	975	149	92	74	0	0	0	0
1	262	59	42	21	0	0	0	0
2	178	24	14	14	0	0	0	0
3	332	56	15	45	0	1	0	0
4	140	45	16	35	0	1	0	0
Subtotal	912	184	87	115	0	2	0	0

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1	111	30	5	25	0	0	0	0
2	143	31	7	27	0	0	0	0
3	101	28	6	24	0	0	0	0
4	101	36	16	30	0	0	0	0
Subtotal	456	125	34	106	0	0	0	0
1	150	43	15	39	0	0	0	0
2	103	32	6	27	0	0	0	0
3	79	24	6	22	0	0	0	0
4	149	36	14	29	0	0	0	0
Subtotal	481	135	41	117	0	0	0	0
1	110	29	12	20	0	0	0	0
2	80	51	9	44	0	5	0	0
3	87	49	10	43	0	2	0	0
4	407	31	13	25	0	0	0	0
Subtotal	684	160	44	132	0	7	0	0
1	141	71	33	45	0	3	0	0
2	67	33	9	26	0	0	0	0
3	65	31	8	27	0	0	0	0
4	382	16	5	11	0	2	0	0
Subtotal	655	151	55	109	0	5	0	0
1	21	13	5	7	0	1	0	0
2	23	17	6	15	0	1	0	0
3	14	12	3	11	0	1	0	0
4	242	9	1	8	0	1	0	0
Subtotal	300	51	15	41	0	4	0	0
1	28	20	4	17	0	1	0	0
2	24	12	3	8	0	3	0	0
3	23	9	2	6	0	4	0	0
4	203	15	3	11	0	3	0	0
Subtotal	278	56	12	42	0	11	0	0

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1	25	11	1	10	0	1	0	0
2	28	12	2	10	0	2	0	0
3	27	19	3	15	0	3	0	0
4	42	16	6	10	0	1	0	0
Subtotal	122	58	12	45	0	7	0	0
1	48	13	1	12	0	3	0	0
2	56	25	3	24	0	1	0	0
3	16	10	2	10	0	1	0	0
4	194	17	2	13	0	2	0	0
Subtotal	314	65	8	59	0	7	0	0
1	34	14	2	9	0	3	0	0
2	51	19	1	17	0	1	0	0
3	19	10	1	8	0	2	0	0
4	227	22	2	18	0	3	0	0
Subtotal	331	65	6	52	0	9	0	0
1	29	18	2	17	0	2	0	0
2	32	17	5	10	0	4	0	0
3	29	11	0	11	0	0	0	1
4	191	24	2	19	0	1	0	3
Subtotal	281	70	9	57	0	7	0	4
1	37	21	1	17	0	0	0	3
2	26	19	2	14	3	0	0	5
3	47	18	2	8	6	1	1	3
4	221	35	2	19	5	0	0	4
Subtotal	331	93	7	58	14	1	1	15
1	63	18	1	14	3	0	0	2
2	53	19	4	15	5	4	0	2
3	38	19	2	10	4	0	0	5
4	326	31	1	14	3	0	0	4
Subtotal	480	87	8	53	15	4	0	13

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1	1001	68	0	9	4	1	0	6
2	45	30	3	14	3	0	0	2
3	273	32	1	11	5	0	0	5
4	320	32	0	8	1	0	0	3
Subtotal	1639	162	4	42	13	1	0	16
1	123	11	1	3	3	0	0	1
2	169	8	1	4	1	0	0	4
3	2	2	0	2	0	0	0	0
4	8	8	0	4	0	0	0	0
Subtotal	302	29	2	13	4	0	0	5
1	18	16	0	6	1	0	0	1
2	8	7	1	4	2	0	0	3
3	22	19	0	3	1	0	1	4
4	10	9	0	3	1	0	0	2
Subtotal	58	51	1	16	5	0	1	10
1	19	8	0	5	0	0	0	0
2	11	8	0	4	0	1	0	3
3	14	12	1	3	0	0	0	1
4	13	11	0	6	2	0	0	1
Subtotal	57	39	1	18	2	1	0	5
1	11	11	2	5	2	0	0	0
Subtotal	11	11	2	5	2	0	0	0
	10484	1855	542	1167	55	66	2	68

Adverse Event Reporting System (AE

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 05/31/2000 - 10:10 am

earch Criteria:

oduct Name(s):

- CIMETIDINE (A)
- CIMETIDINE HYDROCHLORIDE (A)
- TAGAMET (CIMETIDINE) (V)
- TAGAMET (T)
- TAGAMET (V)
- TAGAMET (CIMETIDINE) 400 MG (V)
- TAGAMET (CIMETIDINE) HB (V)
- TAGAMET HB (V)
- TAGAMET HB (CIMETIDINE) (V)
- TAGAMET HB 200 (V)
- TAGAMET HB 200 (CIMETIDINE) (V)
- TAGAMET HB 200 MG SMITHKLINE BEECHAM CONSUMER HEALTHCARE (V)
- TAGAMET HB 200MG (V)
- TAGAMET HB SMITHKLINE BEECHAM CONSUMER HEALTHCARE (V)

anufacturer Type Sender of ISR

Adverse Event Reporting System (AER

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 05/31/2000 - 10:10 am

earch Type: CASE
earch for reactions listed: ANY
DA Revd. Date: From:
eporter Domestic: YES
eporter First Name:
ull Values for Country
emale:
ge Range: From
edWatch Source Study
edWatch Source Health Professional:
xpedited (15-Day) ISR:
A Summary ISR
clude Deactived ISRs
on-Serious Outcome:
vent End Date:
TC Products Only:

Include Concomitant Products:
ISR/Case #:
FDA Revd. Date: To: 03/31/2000
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products
Mfr. Control #:
Sort in Descending Order
Reporter Last Name
Reporter State
Male
Null Gender Value
Age Range: YEAR
MedWatch Source Consumer
Periodic ISR
5 Day ISR
Follow-up
Serious Outcome
Event Start Date:
ReC

on-Excluded Product(s) for Selected Active Ingredient(s):

IMETIDINE (T)
AGAMET HB (T)
METIDINE (V)
IMETINDENE (V)
CIMETIDINE HCL (T)
TAGAMET HB 200 (T)
CIMETIDINE (CIMETIDINE) TABLET 400 MG (V)
TAGAMET HB (V)
MAALOX FAST BLOCKER (T)
ACINIL (V)
CIMETIDINE TABLETS, 400 MG - GENEVA (V)
TAGAMET (T)
CIMETADINE (V)
CIMETIDINE, GA301 (V)

xcluded Product(s) for Selected Active Ingredient(s):

FDA Adverse Event Reporting System (AERS)
Standard Report
All Preferred Terms in Cases

	Count of PTs	Percent of Total	Labeled
Ineffective	759	7.24	U
usion	518	4.94	U
hoea Nos	470	4.48	U
minal Pain Nos	448	4.27	U
ea	380	3.62	U
ecomastia	375	3.58	U
ness (Exc Vertigo)	362	3.45	U
iting Nos	355	3.39	U
atitis Nos	349	3.33	U
ache Nos	329	3.14	U
Interaction Nos	319	3.04	U
mbocytopenia	296	2.82	U
openia Nos	269	2.57	U
epsia	223	2.13	U
ion	218	2.08	U
tia	204	1.95	U
tence	200	1.91	U
mia	198	1.89	U
tic Function Abnormal Nos	191	1.82	U
us	174	1.66	U
Level Nos Above Therapeutic	151	1.44	U
aria Nos	151	1.44	U
lence	140	1.34	U
Pain	138	1.32	U
ition Aggravated	130	1.24	U
cia	129	1.23	U
cination Nos	129	1.23	U
ssion Nec	128	1.22	U
noea Nos	125	1.19	U
Nos	120	1.14	U
t Pain	113	1.08	U
l Creatinine Increased	108	1.03	U
mia Nec	106	1.01	U
sthesia Nec	105	1.00	U
nusness	102	0.97	U
lension	99	0.94	U
	96	0.92	U
itis Nos	96	0.92	U

	Count of PTs	Percent of Total	Labeled
ing Abnormal Nec	96	0.92	U
;ia	94	0.90	U
tension Nos	93	0.89	U
cardia Nos	92	0.88	U
sensitivity Nos	91	0.87	U
intestinal Haemorrhage Nos	87	0.83	U
itis Nos	87	0.83	U
ılsions Nos	86	0.82	U
pation	84	0.80	U
louth	84	0.80	U
Jedema	84	0.80	U
;e	84	0.80	U
r Nec	82	0.78	U
ing Increased	81	0.77	U
otic Disorder Nos	80	0.76	U
ty Nec	77	0.73	U
sia Nec	75	0.72	U
ulocytosis	74	0.71	U
lgia	71	0.68	U
ıonia Nos	70	0.67	U
Disturbance	70	0.67	U
ion	68	0.65	U
ıgitis Nos	68	0.65	U
ıia Nos	67	0.64	U
opia Nos	66	0.63	U
topenia	65	0.62	U
ombin Level Decreased	64	0.61	U
ıa Nos	60	0.57	U
atitis Nos	60	0.57	U
Nos	60	0.57	U
Pain	57	0.54	U
Maculo-Papular	57	0.54	U
Alkaline Phosphatase Nos Increased	56	0.53	U
ations	56	0.53	U
mal Dreams	55	0.52	U
ım	54	0.52	U
Bilirubin Increased	53	0.51	U
Urea Increased	53	0.51	U

Standard Report
All Preferred Terms in Cases

	Count of PTs	Percent of Total	Labeled
liac Arrest	53	0.51	U
ictorrhoea	53	0.51	U
odilatation	53	0.51	U
lycardia Nos	52	0.50	U
cope	52	0.50	U
ema Peripheral	51	0.49	U
idice Cholestatic	50	0.48	U
onality Disorder Nos	50	0.48	U
dice Nos	49	0.47	U
do Decreased	49	0.47	U
al Failure Nos	49	0.47	U
rtate Aminotransferase Increased	48	0.46	U
ma Nos	48	0.46	U
a Nec	48	0.46	U
or	48	0.46	U
ary Retention	48	0.46	U
rointestinal Disorder Nos	46	0.44	U
ythmia Nos	43	0.41	U
st Enlargement	43	0.41	U
rtonia	43	0.41	U
ary Frequency	42	0.40	U
ena	41	0.39	U
ophilia (Exc Pulmonary)	40	0.38	U
cardial Infarction	40	0.38	U
ea	39	0.37	U
atitis	39	0.37	U
stic Anaemia	38	0.36	U
Marrow Depression Nos	38	0.36	U
ine Aminotransferase Increased	37	0.35	U
hagia	37	0.35	U
al Abnormality Nos	37	0.35	U
tion Nos	37	0.35	U
l Failure Acute	37	0.35	U
itus	37	0.35	U
n Abnormal Neo	37	0.35	U
exia	36	0.34	U
itis Nos	36	0.34	U
pyramidal Disorder Nec	36	0.34	U

	Count of PTs	Percent of Total	Labeled
Accidental Overdose	36	0.34	U
s	36	0.34	U
ition	35	0.33	U
s Nec	34	0.32	U
oma Nos	34	0.32	U
ity	34	0.32	U
Impairment Nos	34	0.32	U
tis Nos	33	0.31	U
is Nos	33	0.31	U
litis Nos	32	0.31	U
t Decreased	32	0.31	U
tis Nos	31	0.30	U
luable Reaction	31	0.30	U
neurotic Oedema	30	0.29	U
mosis	30	0.29	U
esthesia	30	0.29	U
atraemia	30	0.29	U
atory Test Abnormal Nos	30	0.29	U
orrhage Nos	29	0.28	U
glycaemia Nos	29	0.28	U
nza Like Illness	29	0.28	U
hagitis	29	0.28	U
eral Neuropathy Nec	29	0.28	U
Nos	28	0.27	U
ination Abnormal Nos	28	0.27	U
Withdrawal Syndrome	28	0.27	U
aturia Present	28	0.27	U
	27	0.26	U
a Pectoris	26	0.25	U
Discolouration	26	0.25	U
itis Exfoliative Nos	25	0.24	U
ose Nos	25	0.24	U
Disorder Nec	25	0.24	U
Circulatory Failure	24	0.23	U
	24	0.23	U
xi	24	0.23	U
intestinal Tract Cancer Nos	24	0.23	U
olytic Anaemia Nos	24	0.23	U

	Count of PTs	Percent of Total	Labeled
gospasm	24	0.23	U
cytosis Nos	24	0.23	U
vascular Disorder Nos	23	0.22	U
l Nervous System Depression Nos	23	0.22	U
tis	23	0.22	U
Mal Convulsion	23	0.22	U
henic Syndrome	23	0.22	U
Neoplasm Nos	22	0.21	U
bs Positive Haemolytic Anaemia	22	0.21	U
evel Nos Below Therapeutic	22	0.21	U
atory Test Interference Nos	22	0.21	U
Abnormal Nos	22	0.21	U
o Nec	22	0.21	U
ylactic Reaction	21	0.20	U
ntal Overdose (Therapeutic Agent)	20	0.19	U
Amylase Increased	20	0.19	U
ystitis Nos	20	0.19	U
bnormal Nos	20	0.19	U
temesis	20	0.19	U
olysis Nos	20	0.19	U
Ventricular Failure	20	0.19	U
t Increased	20	0.19	U
nctivitis Nec	19	0.18	U
ia	19	0.18	U
ystic Breast Disease	19	0.18	U
kalaemia	19	0.18	U
lycaemia Nos	19	0.18	U
alaemia	19	0.18	U
Depressive Disorder Nos	19	0.18	U
e Twitching	19	0.18	U
y Tract Infection Nos	19	0.18	U
ovascular Accident Nos	18	0.17	U
ocellular Damage	18	0.17	U
ficiency Anaemia	18	0.17	U
ine Nos	18	0.17	U
tis	18	0.17	U
tic Disorder Nos	18	0.17	U
ular Disorder Nos	18	0.17	U

	Count of PTs	Percent of Total	Labeled
)sis Nos	17	0.16	U
l Lactate Dehydrogenase Increased	17	0.16	U
ema Multiforme	17	0.16	U
athic Thrombocytopenic Purpura	17	0.16	U
l Bleeding	17	0.16	U
rotic Syndrome	16	0.15	U
oia	16	0.15	U
ratory Disorder Nos	16	0.15	U
Disorder Nos	16	0.15	U
l Creatine Phosphokinase Increased	15	0.14	U
pia	15	0.14	U
nia	15	0.14	U
ain	15	0.14	U
Disorder Nos	15	0.14	U
mia	15	0.14	U
iae	15	0.14	U
le Attempt	15	0.14	U
ry Incontinence	15	0.14	U
minal Distension	14	0.13	U
orrhoea Nos	14	0.13	U
entricular Block Nos	14	0.13	U
ntia Nos	14	0.13	U
sonalisation	14	0.13	U
atitis Bullous	14	0.13	U
vitis	14	0.13	U
kinetic Syndrome	14	0.13	U
ieri l Vascular Disease Nos	14	0.13	U
ie Oedema	14	0.13	U
inuria Present	13	0.12	U
sis Nos	13	0.12	U
ic Failure Nos	13	0.12	U
lithiasis	13	0.12	U
bs Direct Test Positive	13	0.12	U
nal Perforation	13	0.12	U
ism	13	0.12	U
calcaemia	13	0.12	U
lipidaemia Nos	13	0.12	U
Disorder Nos	13	0.12	U

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	Count of PTs	Percent of Total	Labeled
: Cramps	13	0.12	U
Ulcer	13	0.12	U
is Nos	13	0.12	U
ected Therapeutic Effect	13	0.12	U
Fibrillation	12	0.11	U
	12	0.11	U
Thromboplastin Decreased	12	0.11	U
ct Nec	12	0.11	U
Nos	12	0.11	U
es Insipidus	12	0.11	U
nal Disturbance Nos	12	0.11	U
ma Nodosum	12	0.11	U
ocyte Sedimentation Rate Increased	12	0.11	U
ma Nos	12	0.11	U
Nos	12	0.11	U
roteinaemia	12	0.11	U
nia	12	0.11	U
adenopathy	12	0.11	U
sm Nos	12	0.11	U
us Nos	12	0.11	U
P in Nos	12	0.11	U
ia	12	0.11	U
ic Lupus Erythematosus	12	0.11	U
: Discolouration Nos	12	0.11	U
y Tract Disorder Nos	12	0.11	U
nt Nos	11	0.10	U
al Ischaemia	11	0.10	U
s Nos	11	0.10	U
ss Nos	11	0.10	U
lependence	11	0.10	U
: Ulcer	11	0.10	U
Zoster	11	0.10	U
ne Level Nos Abnormal	11	0.10	U
a Nos	11	0.10	U
entricular Block Complete	10	0.10	U
itis Nos	10	0.10	U
us Renal Nos	10	0.10	U
is	10	0.10	U

	Count of PTs	Percent of Total	Labeled
nital Abnormality Nos	10	0.10	U
es Mellitus Nos	10	0.10	U
Effect Increased	10	0.10	U
Maladministration	10	0.10	U
nitis	10	0.10	U
isorder Nos	10	0.10	U
: Ulcer Perforation	10	0.10	U
	10	0.10	U
c Cirrhosis Nos	10	0.10	U
alcaemia	10	0.10	U
on Site Reaction Nos	10	0.10	U
ul Obstruction Nos	10	0.10	U
Ulceration	10	0.10	U
al Hypotension	10	0.10	U
n ry Embolism	10	0.10	U
nary Oedema Nos	10	0.10	U
Disorder Nos	10	0.10	U
y Hypersecretion	10	0.10	U
megaly	10	0.10	U
la Nos	9	0.09	U
ration	9	0.09	U
in	9	0.09	U
nal Ulcer Haemorrhage	9	0.09	U
nal Ulcer Perforation	9	0.09	U
e Abnormality Nos	9	0.09	U
a-Glutamyltransferase Increased	9	0.09	U
isorder Nos	9	0.09	U
c Necrosis	9	0.09	U
megaly	9	0.09	U
opriate Adh Secretion	9	0.09	U
cal Oedema	9	0.09	U
ual Disorder Nos	9	0.09	U
ain	9	0.09	U
hesia Circumoral	9	0.09	U
is Nos	9	0.09	U
entricular Tachycardia	9	0.09	U
l Haemorrhage	9	0.09	U
ular Tachycardia	9	0.09	U

PT	Count of PTs	Percent of Total	Labeled
Visual Field Defect Nos	9	0.09	U
Antinuclear Factor Positive	8	0.08	U
Apathy	8	0.08	U
Atrioventricular Block Second Degree	8	0.08	U
Cardiospasm	8	0.08	U
Coagulation Disorder Nos	8	0.08	U
Delusion Nos	8	0.08	U
Difficulty In Micturition	8	0.08	U
Gastric Ulcer Haemorrhage	8	0.08	U
Hepatorenal Syndrome	8	0.08	U
Hypophosphataemia	8	0.08	U
Leukaemia Nos	8	0.08	U
Lymphocytosis	8	0.08	U
Myopathy	8	0.08	U
Peritonitis	8	0.08	U
Pleural Effusion	8	0.08	U
Renal Colic	8	0.08	U
Rheumatoid Arthritis	8	0.08	U
Taste Loss	8	0.08	U
Blood Prolactin Increased	7	0.07	U
Cyanosis Nos	7	0.07	U
Ejaculation Disorder Nos	7	0.07	U
Electroencephalogram Abnormal	7	0.07	U
Euphoric Mood	7	0.07	U
Eye Haemorrhage Nec	7	0.07	U
Gastrointestinal Candidiasis	7	0.07	U
Gingival Bleeding	7	0.07	U
Hypercholesterolaemia	7	0.07	U
Hyperpituitarism Nos	7	0.07	U
Hypoventilation	7	0.07	U
Liver Fatty	7	0.07	U
Menometrorrhagia	7	0.07	U
Micturition Urgency	7	0.07	U
Oral Candidiasis	7	0.07	U
Parotid Gland Enlargement	7	0.07	U
Pericardial Effusion	7	0.07	U
Pneumonitis Aspiration	7	0.07	U
Sinus Bradycardia	7	0.07	U

PT	Count of PTs	Percent of Total	Labeled
Acute Myeloid Leukaemia Nos	6	0.06	U
Alcohol Intolerance	6	0.06	U
Appetite Increased	6	0.06	U
Blood Dyscrasia Nos	6	0.06	U
Cyst Nos	6	0.06	U
Diarrhoea Haemorrhagic	6	0.06	U
Dysarthria	6	0.06	U
Earache	6	0.06	U
Eczema Nos	6	0.06	U
Epididymitis Nos	6	0.06	U
Hiccups	6	0.06	U
Hypopituitarism	6	0.06	U
Hypothermia	6	0.06	U
Immune System Disorder Nos	6	0.06	U
Infertility Male	6	0.06	U
Injection Site Pain	6	0.06	U
Joint Disorder Nos	6	0.06	U
Keratoconjunctivitis	6	0.06	U
Lymphoma Nos	6	0.06	U
Mastitis	6	0.06	U
Mydriasis	6	0.06	U
Pallor	6	0.06	U
Photosensitivity Reaction Nos	6	0.06	U
Serum Sickness	6	0.06	U
Stevens Johnson Syndrome	6	0.06	U
Thrombosis Nos	6	0.06	U
Tolerance Increased	6	0.06	U
Tooth Caries Nos	6	0.06	U
Vascular Disorder Nos	6	0.06	U
Ventricular Arrhythmia Nos	6	0.06	U
Ventricular Fibrillation	6	0.06	U
Weakness	6	0.06	U
White Blood Cell Disorder Nos	6	0.06	U
Abortion Nos	5	0.05	U
Adrenal Insufficiency Nos	5	0.05	U
Aspermia	5	0.05	U
Benign Intracranial Hypertension	5	0.05	U
Bleeding Time Prolonged	5	0.05	U

PT	Count of PTs	Percent of Total	Labeled
Bundle Branch Block Nos	5	0.05	U
Cellulitis	5	0.05	U
Cholangitis Nos	5	0.05	U
Dry Eye Nec	5	0.05	U
Dysphonia	5	0.05	U
Enlarged Clitoris	5	0.05	U
Gangrene Nos	5	0.05	U
Glycosuria Present	5	0.05	U
Haemoptysis	5	0.05	U
Haemorrhagic Stroke	5	0.05	U
Hemiplegia	5	0.05	U
Lung Cancer Stage Unspecified (Exc Metastatic Tumours To Lung)	5	0.05	U
Megaloblastic Anaemia Nos	5	0.05	U
Movement Disorder Nos	5	0.05	U
Neurosis Nos	5	0.05	U
Nocturia	5	0.05	U
Orchitis Nos	5	0.05	U
Photophobia	5	0.05	U
Pyuria	5	0.05	U
Retroperitoneal Fibrosis	5	0.05	U
Salivary Gland Enlargement Nos	5	0.05	U
Seborrhoea	5	0.05	U
Sialoadenitis Nos	5	0.05	U
Skin Disorder Nos	5	0.05	U
Sleep Disorder Nos	5	0.05	U
Tenosynovitis	5	0.05	U
Torsade De Pointes	5	0.05	U
Vascular Purpura	5	0.05	U
Vestibular Disorder Nos	5	0.05	U
Abdominal Pain Upper	4	0.04	U
Abscess Nos	4	0.04	U
Accommodation Disorder	4	0.04	U
Arteriosclerosis	4	0.04	U
Arteritis Nos	4	0.04	U
Arthrosis Nos	4	0.04	U
Blindness Nec	4	0.04	U
Blood Magnesium Decreased	4	0.04	U

PT	Count of PTs	Percent of Total	Labeled
Breast Engorgement	4	0.04	U
Choreoathetosis	4	0.04	U
Dermatitis Lichenoid	4	0.04	U
Digoxin Toxicity	4	0.04	U
Drug Toxicity Nos	4	0.04	U
Dyskinesia Nec	4	0.04	U
Electrocardiogram Qt Prolonged	4	0.04	U
Feminization	4	0.04	U
Gastric Atony	4	0.04	U
Gingival Hyperplasia	4	0.04	U
Glomerulonephritis Nos	4	0.04	U
Halitosis	4	0.04	U
Hepatic Failure	4	0.04	U
Hyperaesthesia	4	0.04	U
Hyperchloraemia	4	0.04	U
Hypernatraemia	4	0.04	U
Hyperthyroidism	4	0.04	U
Hyperuricaemia	4	0.04	U
Hypokinesia	4	0.04	U
Hypoxia	4	0.04	U
Infertility Female	4	0.04	U
Injection Site Inflammation	4	0.04	U
Mania	4	0.04	U
Mucous Membrane Disorder Nos	4	0.04	U
Multiple Sclerosis	4	0.04	U
Muscle Atrophy	4	0.04	U
Oesophageal Ulcer	4	0.04	U
Oliguria	4	0.04	U
Polyneuropathy Nos	4	0.04	U
Prothrombin Level Increased	4	0.04	U
Sexual Dysfunction Nos	4	0.04	U
Skin Depigmentation	4	0.04	U
Skin Necrosis	4	0.04	U
Stridor	4	0.04	U
Thrombotic Thrombocytopenic Purpura	4	0.04	U
Tongue Disorder Nos	4	0.04	U
Unintended Pregnancy	4	0.04	U
Vaginitis	4	0.04	U

PT	Count of PTs	Percent of Total	Labeled
Ventricular Extrasystoles	4	0.04	U
Anaemia Folate Deficiency	3	0.03	U
Anaemia Vitamin B12 Deficiency	3	0.03	U
Ascites	3	0.03	U
Atelectasis	3	0.03	U
Blood Electrolytes Nos Abnormal	3	0.03	U
Blood Potassium Decreased	3	0.03	U
Bone Pain	3	0.03	U
Cardiomegaly Nos	3	0.03	U
Cerebral Infarction	3	0.03	U
Cerebral Oedema	3	0.03	U
Coagulation Time Nos Prolonged	3	0.03	U
Congenital Musculoskeletal Abnormality Nos	3	0.03	U
Coronary Artery Disease Nos	3	0.03	U
Deafness Transitory	3	0.03	U
Disorder Neonatal Nos	3	0.03	U
Faecal Incontinence	3	0.03	U
Furuncle (Exc Genital)	3	0.03	U
Gastritis Haemorrhagic	3	0.03	U
Gastroenteritis Nos	3	0.03	U
Gastrointestinal Necrosis	3	0.03	U
Hair Colour Changes	3	0.03	U
Hangover (Exc Alcohol)	3	0.03	U
Heart Rate Increased	3	0.03	U
Hepatic Neoplasm Malignant Nos	3	0.03	U
Injection Site Hypersensitivity	3	0.03	U
Injection Site Oedema	3	0.03	U
Intracranial Haemorrhage Nos	3	0.03	U
Keratitis Nec	3	0.03	U
Lactic Acidosis	3	0.03	U
Lipase Increased	3	0.03	U
Loss Of Consciousness Nec	3	0.03	U
Macrocytic Anaemia Nos	3	0.03	U
Meningitis Nos	3	0.03	U
Menorrhagia	3	0.03	U
Methaemoglobinaemia Nos	3	0.03	U
Miosis	3	0.03	U
Muscle Spasms	3	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Neck Stiffness	3	0.03	U
Oesophageal Haemorrhage	3	0.03	U
Oesophageal Stenosis	3	0.03	U
Optic Neuritis Nec	3	0.03	U
Otitis Media Nos	3	0.03	U
Pancreatic Disorder Nos	3	0.03	U
Papilloedema	3	0.03	U
Parathyroid Disorder Nos	3	0.03	U
Pathological Fracture	3	0.03	U
Penile Disorder Nos	3	0.03	U
Peptic Ulcer Haemorrhage	3	0.03	U
Peptic Ulcer Perforation	3	0.03	U
Pericarditis Nos	3	0.03	U
Pleural Disorder Nos	3	0.03	U
Polycythaemia Nos	3	0.03	U
Pulmonary Eosinophilia	3	0.03	U
Pulmonary Haemorrhage	3	0.03	U
Rash Pruritic	3	0.03	U
Renal Tubular Necrosis	3	0.03	U
Respiratory Acidosis	3	0.03	U
Scrotal Oedema	3	0.03	U
Skin Ulcer Nos	3	0.03	U
Tenesmus	3	0.03	U
Testicular Atrophy	3	0.03	U
Thrombocythaemia	3	0.03	U
Tooth Abscess	3	0.03	U
Trismus	3	0.03	U
Vaginal Candidiasis	3	0.03	U
Yawning	3	0.03	U
Acute Abdomen	2	0.02	U
Acute Myelomonocytic Leukaemia	2	0.02	U
Adenoma Benign Nos	2	0.02	U
Akathisia	2	0.02	U
Amyloidosis Nos	2	0.02	U
Anovulatory Cycle	2	0.02	U
Anticholinergic Syndrome	2	0.02	U
Blood In Stool	2	0.02	U
Blood Pressure Increased	2	0.02	U

	Count of PTs	Percent of Total	Labeled
ine Disorder Nos	2	0.02	U
irsitis	2	0.02	U
ntral Nervous System Stimulation Nos	2	0.02	U
olitis Ulcerative	2	0.02	U
ngenital Central Nervous System Anomaly	2	0.02	U
is			
oombs Negative Haemolytic Anaemia	2	0.02	U
r Pulmonale Nos	2	0.02	U
rneal Lesion Nos	2	0.02	U
eatinine Renal Clearance Decreased	2	0.02	U
ystalluria Present	2	0.02	U
rmatitis Contact	2	0.02	U
smenorrhoea	2	0.02	U
r Disorder Nos	2	0.02	U
ectrocardiogram Abnormal Nos	2	0.02	U
cephalitis Nos	2	0.02	U
docarditis Nos	2	0.02	U
idermal Necrolysis	2	0.02	U
traocular Muscle Paresis	2	0.02	U
elid Ptosis	2	0.02	U
ted Eruption	2	0.02	U
ushing	2	0.02	U
it Festinating	2	0.02	U
nital Oedema Nos	2	0.02	U
nadotrophin Increased	2	0.02	U
anuloma Nos	2	0.02	U
emoglobin Decreased	2	0.02	U
patic Encephalopathy	2	0.02	U
patitis C	2	0.02	U
patosplenomegaly	2	0.02	U
dronephrosis	2	0.02	U
perventilation	2	0.02	U
pogammaglobulinaemia Nos	2	0.02	U
poplastic Anaemia	2	0.02	U
pothyroidism	2	0.02	U
povitaminosis Nos	2	0.02	U
estinal Ulcer	2	0.02	U
crimal Disorder Nos	2	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Limb Reduction Defect	2	0.02	U
Marrow Hyperplasia	2	0.02	U
Megakaryocytes Abnormal	2	0.02	U
Mental Disorder Nec	2	0.02	U
Mental Impairment Nos	2	0.02	U
Mental Retardation Severity Unspecified	2	0.02	U
Microcytic Anaemia	2	0.02	U
Muscle Rigidity	2	0.02	U
Myelofibrosis	2	0.02	U
Myocardial Ischaemia	2	0.02	U
Myocarditis Nos	2	0.02	U
Myoclonic Jerks	2	0.02	U
Nasal Congestion	2	0.02	U
Necrosis	2	0.02	U
Nephropathy Toxic	2	0.02	U
Neuralgia Nos	2	0.02	U
Oculogyric Crisis	2	0.02	U
Ovarian Disorder Nos	2	0.02	U
Pancreatitis Haemorrhagic	2	0.02	U
Pituitary Tumour Benign Nos	2	0.02	U
Platelet Abnormalities Nos	2	0.02	U
Pneumothorax Nos	2	0.02	U
Polyarteritis Nodosa	2	0.02	U
Premature Baby	2	0.02	U
Priapism	2	0.02	U
Prostate Cancer Nos	2	0.02	U
Pulmonary Fibrosis	2	0.02	U
Pyloric Stenosis Nos	2	0.02	U
Reticuloendothelial System Stimulated	2	0.02	U
Retinal Degeneration	2	0.02	U
Retinal Vascular Disorder Nos	2	0.02	U
Rhabdomyolysis	2	0.02	U
Salicylism	2	0.02	U
Scleritis Nos	2	0.02	U
Scleroderma	2	0.02	U
Screaming	2	0.02	U
Skin Carcinoma Nos	2	0.02	U
Skin Hypertrophy	2	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Skin Neoplasm Nos	2	0.02	U
Sputum Increased	2	0.02	U
Sulphaemoglobinaemia	2	0.02	U
Suppressed Lactation	2	0.02	U
Systemic Lupus Erythematosus Rash	2	0.02	U
Testicular Failure Nec	2	0.02	U
Tetany	2	0.02	U
Thirst	2	0.02	U
Throat Oedema	2	0.02	U
Thrombophlebitis Deep	2	0.02	U
Thyroid Disorder Nos	2	0.02	U
Tolerance Decreased	2	0.02	U
Upper Gastrointestinal Haemorrhage	2	0.02	U
Uterine Disorder Nos	2	0.02	U
Uterine Fibroids	2	0.02	U
Vaginal Discharge	2	0.02	U
Vascular Anomaly Nos	2	0.02	U
Viral Infection Nos	2	0.02	U
Abnormal Behaviour Nos	1	0.01	U
Achlorhydria	1	0.01	U
Acute Lymphocytic Leukaemia	1	0.01	U
Aggression	1	0.01	U
Akinesia	1	0.01	U
Angina Unstable	1	0.01	U
Anhedonia	1	0.01	U
Anorgasmia	1	0.01	U
Antisocial Behaviour	1	0.01	U
Anuria	1	0.01	U
Aphasia	1	0.01	U
Arterial Spasm Nos	1	0.01	U
Asphyxia	1	0.01	U
Atrial Flutter	1	0.01	U
Atrioventricular Block First Degree	1	0.01	U
Bacterial Infection Nos	1	0.01	U
Balanitis Nos	1	0.01	U
Biliary Colic	1	0.01	U
Bilirubinuria	1	0.01	U
Bipolar Disorder Nec	1	0.01	U

T	Count of PTs	Percent of Total	Labeled
ipolar I Disorder	1	0.01	U
ladder Cancer Nos	1	0.01	U
lindness Night	1	0.01	U
lood Acid Phosphatase Increased	1	0.01	U
lood Cholinesterase Decreased	1	0.01	U
lood Creatine Increased	1	0.01	U
ood Creatine Phosphokinase Mb Increased	1	0.01	U
ood Creatinine Decreased	1	0.01	U
ood Gases Nos Abnormal	1	0.01	U
ood Sodium Decreased	1	0.01	U
ood Thromboplastin Increased	1	0.01	U
radykinesia	1	0.01	U
rain Hypoxia	1	0.01	U
reast Tenderness	1	0.01	U
ronchiolitis	1	0.01	U
alcium Metabolism Disorder	1	0.01	U
alculus Bladder	1	0.01	U
apillary Fragility Increased	1	0.01	U
ardiac Disorder Nos	1	0.01	U
arotid Artery Stenosis	1	0.01	U
atatonia	1	0.01	U
erebellar Ataxia	1	0.01	U
erebral Artery Thrombosis	1	0.01	U
erebrovascular Disorder Nos	1	0.01	U
hest Pressure Sensation	1	0.01	U
holangitis Sclerosing	1	0.01	U
holinergic Syndrome	1	0.01	U
hondrodystrophy	1	0.01	U
hronic Myeloid Leukaemia	1	0.01	U
lamminess	1	0.01	U
oagulation Time Nos Shortened	1	0.01	U
olitis Haemorrhagic	1	0.01	U
ollapse	1	0.01	U
olour Blindness Nec	1	0.01	U
ompleted Suicide	1	0.01	U
omplications Of Maternal Exposure To herapuetic Drugs	1	0.01	U
ongenital Clubfoot	1	0.01	U

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T	Count of PTs	Percent of Total	Labeled
onversion Disorder	1	0.01	U
oronary Artery Occlusion	1	0.01	U
sf Abnormal Nos	1	0.01	U
ushing'S Syndrome	1	0.01	U
yanosis Peripheral	1	0.01	U
iabetic Coma Nos	1	0.01	U
iabetic Ketoacidosis	1	0.01	U
iabetic Nephropathy Nos	1	0.01	U
rug Effect Decreased	1	0.01	U
rug Eruption Nos	1	0.01	U
rug Hypersensitivity	1	0.01	U
uodenal Ulcer Reactivated	1	0.01	U
lectrocardiogram Qt Corrected Interval olonged	1	0.01	U
lectrocardiogram St Segment Elevation	1	0.01	U
lectrocardiogram T Wave Inversion	1	0.01	U
lectrolyte Depletion	1	0.01	U
mphysema	1	0.01	U
ncephalopathy Nos	1	0.01	U
ndocrine Disorder Nos	1	0.01	U
ndometrial Cancer Nos	1	0.01	U
ndometrial Hyperplasia	1	0.01	U
ythema Nec	1	0.01	U
ythrocyte Vacuolization	1	0.01	U
ythroid Maturation Arrest	1	0.01	U
trasystoles Nos	1	0.01	U
ecal Occult Blood Positive	1	0.01	U
eces Discoloured	1	0.01	U
ll	1	0.01	U
llot'S Tetralogy	1	0.01	U
tigue	1	0.01	U
eling Cold	1	0.01	U
rtility Increased	1	0.01	U
stric Erosions	1	0.01	U
stric Haemorrhage	1	0.01	U
stric Ulcer Haemorrhage & Perforation	1	0.01	U
stro-Oesophageal Reflux Disease	1	0.01	U
nital Oedema Female	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Genital Pain Male	1	0.01	U
Glucocorticoids Nos Increased	1	0.01	U
Gonadotrophin Deficiency	1	0.01	U
Growth Retarded	1	0.01	U
Guillain Barre Syndrome	1	0.01	U
Haemorrhoids	1	0.01	U
Hallucination, Auditory	1	0.01	U
Hallucinations Aggravated	1	0.01	U
Hepatic Disorder Nos	1	0.01	U
Hepatic Neoplasm Nos	1	0.01	U
Hepatic Pain	1	0.01	U
Hepatitis B Surface Antigen Positive	1	0.01	U
Herpes Simplex	1	0.01	U
Hiatus Hernia	1	0.01	U
High Density Lipoprotein Decreased	1	0.01	U
Hot Flushes Nos	1	0.01	U
Hydrocephalus Nos	1	0.01	U
Hydroureter	1	0.01	U
Hyperacusis	1	0.01	U
Hyperchlorhydria	1	0.01	U
Hypergammaglobulinaemia	1	0.01	U
Hypertrophy Nos	1	0.01	U
Hypervitaminosis Nos	1	0.01	U
Hypochloraemia	1	0.01	U
Hyporeflexia	1	0.01	U
Hypovolaemia	1	0.01	U
Ichthyosis	1	0.01	U
Ileitis	1	0.01	U
Injection Site Atrophy	1	0.01	U
Injection Site Fibrosis	1	0.01	U
Injection Site Haemorrhage	1	0.01	U
International Normalised Ratio Decreased	1	0.01	U
International Normalised Ratio Increased	1	0.01	U
Intestinal Perforation Nos	1	0.01	U
Intestinal Stenosis Nos	1	0.01	U
Iodine Uptake Decreased	1	0.01	U
Jaundice Neonatal	1	0.01	U
Laryngeal Cancer Nos	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Laryngitis Nos	1	0.01	U
Lethargy	1	0.01	U
Leukaemoid Reaction	1	0.01	U
Libido Increased	1	0.01	U
Lip Discolouration	1	0.01	U
Liver Function Tests Nos Abnormal	1	0.01	U
Loin Pain	1	0.01	U
Loose Stools	1	0.01	U
Malabsorption	1	0.01	U
Masked Facies	1	0.01	U
Melanodermia	1	0.01	U
Menopause	1	0.01	U
Mesenteric Occlusion	1	0.01	U
Metabolic Encephalopathy Nos	1	0.01	U
Metal Poisoning	1	0.01	U
Methaemoglobinuria Present	1	0.01	U
Monocytosis	1	0.01	U
Multiple Congenital Abnormalities	1	0.01	U
Multiple Myeloma	1	0.01	U
Neck Oedema	1	0.01	U
Nephrosclerosis	1	0.01	U
Neuroleptic Malignant Syndrome	1	0.01	U
Nodding Of Head	1	0.01	U
Non-Accidental Injury	1	0.01	U
Obesity	1	0.01	U
Oedema Upper Limb	1	0.01	U
Ogomenorrhoea Nos	1	0.01	U
Ophthalmoplegia Nos	1	0.01	U
Oral Soft Tissue Disorder Nos	1	0.01	U
Osteoporosis Nos	1	0.01	U
Ovarian Cancer Nos	1	0.01	U
Pancreatitis Necrotising	1	0.01	U
Panophthalmitis	1	0.01	U
Paraplegia	1	0.01	U
Pathogen Resistance	1	0.01	U
Pituitary Tumour Nos*	1	0.01	U
Placental Disorder Nos	1	0.01	U
Platelet Count Decreased	1	0.01	U

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PT	Count of PTs	Percent of Total	Labeled
Polyserositis	1	0.01	U
Proctitis Nos	1	0.01	U
Prothrombin Time Prolonged	1	0.01	U
Pruritus Ani	1	0.01	U
Psoriasis	1	0.01	U
Pulmonary Mycosis	1	0.01	U
Pulmonary Thrombosis Nos	1	0.01	U
Pulsus Bigeminus	1	0.01	U
Pupils Unequal	1	0.01	U
Pyelonephritis Nos	1	0.01	U
Quadriplegia	1	0.01	U
Radiation Injury Nos	1	0.01	U
Rash Generalised	1	0.01	U
Rash Papular	1	0.01	U
Rash Pustular	1	0.01	U
Rash Vesicular	1	0.01	U
Red Blood Cell Abnormality Nos	1	0.01	U
Refractive Errors Nos	1	0.01	U
Refractory Anaemia	1	0.01	U
Renal Papillary Necrosis	1	0.01	U
Renal Vasculitis	1	0.01	U
Retinal Artery Thrombosis	1	0.01	U
Retinal Disorder Nos	1	0.01	U
Retinal Haemorrhage	1	0.01	U
Retinal Vein Thrombosis	1	0.01	U
Road Traffic Accident	1	0.01	U
Sarcoidosis Nos	1	0.01	U
Sarcoma Nos	1	0.01	U
Septic Arthritis Nos	1	0.01	U
Sickness	1	0.01	U
Skin Fungal Infection Nos	1	0.01	U
Skin Nodule	1	0.01	U
Skin Odour Abnormal	1	0.01	U
Skin Striae	1	0.01	U
Small Intestinal Perforation Nos	1	0.01	U
Staphylococcal Impetigo	1	0.01	U
Streptococcal Infection Nos	1	0.01	U
Subarachnoid Haemorrhage Nos	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Subcutaneous Nodule	1	0.01	U
Subdural Haematoma	1	0.01	U
Sudden Death Unexplained	1	0.01	U
Superinfection	1	0.01	U
Supraventricular Arrhythmia Nos	1	0.01	U
Supraventricular Extrasystoles	1	0.01	U
Tardive Dyskinesia	1	0.01	U
Tendon Disorder Nos	1	0.01	U
Throat Tightness	1	0.01	U
Thrombophlebitis Superficial	1	0.01	U
Thyroid Adenoma Nos	1	0.01	U
Thyroiditis Nos	1	0.01	U
Tricuspid Valve Incompetence	1	0.01	U
Tuberculosis Nos Aggravated	1	0.01	U
Ulcer Haemorrhage Nos	1	0.01	U
Uterine Haemorrhage	1	0.01	U
Uterine Neoplasm Nos	1	0.01	U
Venous Thrombosis Deep Limb	1	0.01	U
Ventricular Hypertrophy	1	0.01	U
Vision Blurred	1	0.01	U
Vitreous Disorder Nos	1	0.01	U
Vomiting Neonatal	1	0.01	U
Water Intoxication	1	0.01	U
White Blood Cell Count Increased	1	0.01	U

Adverse Event Reporting System (AERS)

Standard Report

Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 05/31/2000 - 12:50 pm

Search Criteria:

Product Name(s):

FAMOTIDINE (A)
PEPCID (FAMOTIDINE) (V)
PEPCID (T)
PEPCID AC (V)
PEPCID AC 10 MG FAMOTIDINE TABLETS (V)
PEPCID (AC (FAMOTIDINE 10MG) CHEWABLE TAB (V)
PEPCID AC (FAMOTIDINE 10 MG) CHEWABLE TAB (V)
PEPCID AC (FAMOTIDINE 10 MG) GELCAPS (V)
PEPCID AC (FAMOTIDINE 10 MG) TABLETS (V)
PEPCID AC (FAMOTIDINE) (V)

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Manufacturer Type: Sender of ISR
Search Type: CASE
Search for reactions listed: ANY
FDA Rcvd. Date: From:
Reporter Domestic: YES
Reporter First Name:
Null Values for Country
Female:
Age Range: From
MedWatch Source Study
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
RA Summary ISR
Include Deactived ISRs
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #:
FDA Rcvd. Date: To: 03/31/2000
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products
Mfr. Control #:
Sort in Descending Order
Reporter Last Name
Reporter State
Male
Null Gender Value
Age Range: YEAR
MedWatch Source Consumer
Periodic ISR
5 Day ISR
Follow-up
Serious Outcome
Event Start Date:
ReC

dverse Ev...t Reporting System (AER

Standard Report

Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 05/31/2000 - 12:50 pm

Non-Excluded Product(s) for Selected Active Ingredient(s):

FAMOTDINE (T)
PEPCID IV PRESERVATIVE FREE (T)
FAMOTIDINE 20MG MERCK (V)
GASTER (V)
GASTER INF (V)
PEPCIDIN (V)
PEPDUL SOLUTION FOR INJECTION (V)
FAMOTIDINE (T)
PEPCID PRESERVATIVE FREE (T)
FAMOTIDINE (AMFAMOX) (V)
GASTER (FAMOTIDINE) (V)
GASTER(FAMOTIDINE) TABLET (V)
PEPDUL (V)
PEPDUL TABLETS (V)
PEPCID (T)
AMFAMOX (FAMOTIDINE) (V)
FAMOTIDINE (PEPDINE) TABLETS (V)
GASTER (FAMOTIDINE) TABLET (V)
MYLANTA AR (V)
PEPDUL (FAMOTIDINE) (V)
PEPCID AC (T)
FAMOTIDINE (V)
FAMOTIDINE 20MG IV BID (V)
GASTER 10 (V)
PDPDUL SOLUTION FOR INJECTION (V)
PEPDUL (FAMOTIDINE) AMPOULE (V)

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
987	1	9	2	0	2	0	0	0	0
	2	59	7	0	7	0	0	0	0
	3	51	6	2	5	0	0	0	0
	4	28	6	1	6	0	0	0	0
	Subtotal	147	21	3	20	0	0	0	0
988	1	36	5	1	4	0	0	0	0
	2	34	7	1	7	0	0	0	0
	3	39	9	3	7	0	0	0	0
	4	33	11	0	11	0	0	0	0
	Subtotal	142	32	5	29	0	0	0	0
989	1	67	26	1	24	0	1	0	0
	2	67	11	0	10	0	1	0	0
	3	81	1	0	1	0	0	0	0
	4	54	14	0	14	0	0	0	0
	Subtotal	269	52	1	49	0	2	0	0
990	1	9	4	2	3	0	0	0	0
	2	18	11	0	7	0	5	0	0
	3	8	2	0	1	0	1	0	0
	4	177	31	0	30	0	1	0	0
	Subtotal	212	48	2	41	0	7	0	0
991	1	28	7	0	7	0	0	0	0
	2	8	2	0	2	0	0	0	0
	3	18	8	2	8	0	0	0	0
	4	143	20	0	19	0	1	0	0
	Subtotal	197	37	2	36	0	1	0	0
992	1	20	11	2	9	0	1	0	0
	2	24	13	1	12	0	0	0	0
	3	8	1	1	1	0	0	0	0
	4	115	15	1	13	0	1	0	0
	Subtotal	167	40	5	35	0	2	0	0

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1993	1	16	4	1	3	0	0	0	0
	2	14	4	1	4	0	0	0	0
	3	15	10	2	9	0	0	0	0
	4	134	9	0	7	1	0	0	1
	Subtotal	179	27	4	23	1	0	0	1
1994	1	36	15	1	15	2	0	0	0
	2	16	9	0	8	0	1	0	1
	3	15	12	1	10	1	2	0	0
	4	131	13	0	9	3	0	1	2
	Subtotal	198	49	2	42	6	3	1	3
1995	1	21	6	1	5	0	0	0	0
	2	15	12	0	5	2	0	0	2
	3	16	16	0	11	4	0	0	0
	4	212	19	1	13	1	0	0	3
	Subtotal	264	53	2	34	7	0	0	5
1996	1	1110	975	2	8	1	1	0	3
	2	1018	1002	2	3	3	0	0	2
	3	582	570	2	8	0	0	0	2
	4	742	474	1	12	7	0	0	3
	Subtotal	3452	3021	7	31	11	1	0	10
1997	1	444	433	0	10	2	0	1	4
	2	384	379	1	8	1	0	0	2
	3	1	1	0	1	0	0	0	0
	4	13	11	0	8	1	0	0	1
	Subtotal	842	824	1	27	4	0	1	7
1998	1	9	8	0	5	1	0	1	1
	2	17	11	0	4	1	2	0	2
	3	19	17	2	12	5	0	0	3
	4	13	12	0	6	4	0	0	3
	Subtotal	58	48	2	27	11	2	1	9

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1999	1	39	25	1	14	6	4	0	2
	2	8	8	2	2	3	1	0	0
	3	29	26	3	8	1	2	0	7
	4	35	32	4	16	2	0	0	2
	Subtotal	111	91	10	40	12	7	0	11
2000	1	14	13	1	5	1	0	0	1
	Subtotal	14	13	1	5	1	0	0	1
Total		6252	4356	47	439	53	25	3	47

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Search Criteria Name: CORKENA Search submitted on: 05-31-2000 12:43:02
Product/Group Name: FAMOTIDINE (A)
Reaction/Group Name:
Search Case Count6252

Date - Time: 05/31/2000 - 12:50 pm
Run by: CORKENA

Adverse Event Reporting System (AE

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 05/31/2000 - 01:20 pm

Search Criteria:

Product Name(s):

- FAMOTIDINE (A)
- PEPCID (FAMOTIDINE) (V)
- PEPCID (T)
- PEPCID AC (V)
- PEPCID AC 10 MG FAMOTIDINE TABLETS (V)
- PEPCID (AC (FAMOTIDINE 10MG) CHEWABLE TAB (V)
- PEPCID AC (FAMOTIDINE 10 MG) CHEWABLE TAB (V)
- PEPCID AC (FAMOTIDINE 10 MG) GELCAPS (V)
- PEPCID AC (FAMOTIDINE 10 MG) TABLETS (V)
- PEPCID AC (FAMOTIDINE) (V)

Manufacturer Type Sender of ISR

Search Type: CASE

Search for reactions listed: ANY

FDA Rcvd. Date: From:

Reporter Domestic: YES

Reporter First Name:

Null Values for Country

Female:

Age Range: From

MedWatch Source Study

MedWatch Source Health Professional:

Expedited (15-Day) ISR:

RA Summary ISR

Include Deactived ISRs

Non-Serious Outcome:

Event End Date:

OTC Products Only:

Include Concomitant Products:

ISR/Case #:

FDA Rcvd. Date: To: 03/31/2000

Reporter Foreign:

Reporter City:

Patient ID:

Gender Unknown:

Age Range: To:

MedWatch Source Literature

Direct ISR:

10 Day ISR:

Initial:

Processed ISRs/Cases Only: YES

ISRs with No Outcome Reported:

DeC:

Include Combination Products

Mfr. Control #:

Sort in Descending Order

Reporter Last Name

Reporter State

Male

Null Gender Value

Age Range: YEAR

MedWatch Source Consumer

Periodic ISR

5 Day ISR

Follow-up

Serious Outcome

Event Start Date:

ReC

Adverse Event Reporting System (AE...

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 05/31/2000 - 01:20 pm

Non-Excluded Product(s) for Selected Active Ingredient(s):

FAMOTDINE (T)	FAMOTIDINE (T)	PEPCID (T)	PEPCID AC (T)
PEPCID IV PRESERVATIVE FREE (T)	PEPCID PRESERVATIVE FREE (T)	AMFAMOX (FAMOTIDINE) (V)	FAMOTIDINE (V)
FAMOTIDINE 20MG MERCK (V)	FAMOTIDINE (AMFAMOX) (V)	FAMOTIDINE (PEPDINE) TABLETS (V)	FAMOTIDINE 20MG IV BID (V)
GASTER (V)	GASTER (FAMOTIDINE) (V)	GASTER (FAMOTIDINE) TABLET (V)	GASTER 10 (V)
GASTER INF (V)	GASTER(FAMOTIDINE) TABLET (V)	MYLANTA AR (V)	PDPDUL SOLUTION FOR INJECTION (V)
PEPCIDIN (V)	PEPDUL (V)	PEPDUL (FAMOTIDINE) (V)	PEPDUL (FAMOTIDINE) AMPOULE (V)
PEPDUL SOLUTION FOR INJECTION (V)	PEPDUL TABLETS (V)		

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Drug Ineffective	821	13.13	U
Diarrhoea Nos	537	8.59	U
Abdominal Pain Nos	320	5.12	U
Constipation	318	5.09	U
Dermatitis Nos	314	5.02	U
Dizziness (Exc Vertigo)	311	4.97	U
Headache Nos	304	4.86	U
Nausea	265	4.24	U
Pruritus	262	4.19	U
Confusion	215	3.44	U
Thrombocytopenia	204	3.26	U
Insomnia Nec	154	2.46	U
Dyspepsia	140	2.24	U
Flatulence	132	2.11	U
Vomiting Nos	131	2.10	U
Alopecia	123	1.97	U
Faecal Abnormality Nos	119	1.90	U
Hallucination Nos	115	1.84	U
Sedation	110	1.76	U
Hypertension Nos	109	1.74	U
Nervousness	108	1.73	U
Dry Mouth	104	1.66	U
Urticaria Nos	103	1.65	U
Asthenia	100	1.60	U
Face Oedema	87	1.39	U
Paraesthesia Nec	80	1.28	U
Taste Disturbance	79	1.26	U
Chest Pain	75	1.20	U
Agitation	73	1.17	U
Dyspnoea Nos	67	1.07	U
Hypersensitivity Nos	66	1.06	U
Pain Nos	64	1.02	U
Tachycardia Nos	62	0.99	U
Palpitations	57	0.91	U
Pyrexia	57	0.91	U
Hepatic Function Abnormal Nos	56	0.90	U
Urinary Frequency	52	0.83	U
Tinnitus	50	0.80	U

PT	Count of PTs	Percent of Total	Labeled
Depression Nec	49	0.78	U
Leucopenia Nos	49	0.78	U
Vasodilatation	49	0.78	U
Drug Interaction Nos	48	0.77	U
Anxiety Nec	44	0.70	U
Melacna	44	0.70	U
Pharyngitis Nos	43	0.69	U
Condition Aggravated	41	0.66	U
Impotence	41	0.66	U
Myalgia	41	0.66	U
Oedema Peripheral	41	0.66	U
Tremor Nec	40	0.64	U
Arthralgia	38	0.61	U
Gynaecomastia	37	0.59	U
Eructation	35	0.56	U
Hyperglycaemia Nos	31	0.50	U
Hypotension	31	0.50	U
Abnormal Dreams	30	0.48	U
Amblyopia Nos	30	0.48	U
Psychotic Disorder Nos	30	0.48	U
Anorexia	28	0.45	U
Hypertonia	28	0.45	U
Amnesia Nec	26	0.42	U
Arrhythmia Nos	26	0.42	U
Cough	26	0.42	U
Muscle Cramps	26	0.42	U
Weight Decreased	26	0.42	U
Accidental Overdose (Therapeutic Agent)	25	0.40	U
Aspartate Aminotransferase Increased	25	0.40	U
Gastrointestinal Haemorrhage Nos	25	0.40	U
Malaise	25	0.40	U
Sweating Increased	25	0.40	U
Blood Bilirubin Increased	24	0.38	U
Gastrointestinal Disorder Nos	24	0.38	U
Alanine Aminotransferase Increased	23	0.37	U
Back Pain	23	0.37	U
Dysphagia	22	0.35	U
Dysuria	22	0.35	U

PT	Count of PTs	Percent of Total	Labeled
Grand Mal Convulsion	22	0.35	U
Oedema Nos	22	0.35	U
Thinking Abnormal Nec	22	0.35	U
Blood Alkaline Phosphatase Nos Increased	21	0.34	U
Delirium	21	0.34	U
Vision Abnormal Nec	21	0.34	U
Blood Creatinine Increased	20	0.32	U
Convulsions Nos	20	0.32	U
Jaundice Nos	20	0.32	U
Unevaluable Reaction	19	0.30	U
Pancreatitis Nos	18	0.29	U
Paranoia	18	0.29	U
Phlebitis Nos	18	0.29	U
Syncope	18	0.29	U
Anaemia Nos	17	0.27	U
Epistaxis	17	0.27	U
Hepatitis Nos	17	0.27	U
Laryngospasm	17	0.27	U
Libido Decreased	17	0.27	U
Stomatitis	17	0.27	U
Urine Abnormal Nos	17	0.27	U
Angioneurotic Oedema	16	0.26	U
Asthma Nos	16	0.26	U
Hostility	16	0.26	U
Jnundice Cholestatic	16	0.26	U
Myasthenic Syndrome	16	0.26	U
Personality Disorder Nos	16	0.26	U
Speech Disorder Nec	16	0.26	U
Conjunctivitis Nec	15	0.24	U
Drug Maladministration	15	0.24	U
Glossitis	15	0.24	U
Haemorrhage Nos	15	0.24	U
Oesophagitis	15	0.24	U
Pancytopenia	15	0.24	U
Rash Maculo-Papular	15	0.24	U
Rhinitis Nos	15	0.24	U
Sepsis Nos	15	0.24	U
Tongue Oedema	15	0.24	U

PT	Count of PTs	Percent of Total	Labeled
Bradycardia Nos	14	0.22	U
Breast Pain	14	0.22	U
Anaphylactic Reaction	13	0.21	U
Arthritis Nos	13	0.21	U
Drug Level Nos Above Therapeutic	13	0.21	U
Rigors	13	0.21	U
Agranulocytosis	12	0.19	U
Delusion Nos	12	0.19	U
Ecchymosis	12	0.19	U
Appetite Increased	11	0.18	U
Blood Lactate Dehydrogenase Increased	11	0.18	U
Bone Marrow Depression Nos	11	0.18	U
Depersonalisation	11	0.18	U
Gamma-Glutamyltransferase Increased	11	0.18	U
Haematuria Present	11	0.18	U
Weight Increased	11	0.18	U
Acne Nos	10	0.16	U
Cardiac Arrest	10	0.16	U
Dehydration	10	0.16	U
Dermatitis Bullous	10	0.16	U
Laboratory Test Abnormal Nos	10	0.16	U
Rectal Bleeding	10	0.16	U
Salivary Hypersecretion	10	0.16	U
Skin Discolouration	10	0.16	U
Central Nervous System Depression Nos	9	0.14	U
Coma Nec	9	0.14	U
Dry Skin	9	0.14	U
Eosinophilia (Exc Pulmonary)	9	0.14	U
Infection Nos	9	0.14	U
Neutropenia	9	0.14	U
Parosmia	9	0.14	U
Platelet Count Decreased	9	0.14	U
Pneumonia Nos	9	0.14	U
Taste Loss	9	0.14	U
Ataxia Nec	8	0.13	U
Peripheral Neuropathy Nec	8	0.13	U
Urinary Tract Infection Nos	8	0.13	U
Acidosis Nos	7	0.11	U

FDA - Adverse Event Reporting System (AERS)
Standard Report
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Blood Urea Increased	7	0.11	U
Cholecystitis Nos	7	0.11	U
Ear Disorder Nos	7	0.11	U
Gait Abnormal Nos	7	0.11	U
Hypoaesthesia	7	0.11	U
Injection Site Reaction Nos	7	0.11	U
Muscle Twitching	7	0.11	U
Myoclonic Jerks	7	0.11	U
Photosensitivity Reaction Nos	7	0.11	U
Renal Failure Nos	7	0.11	U
Respiratory Disorder Nos	7	0.11	U
Ventricular Tachycardia	7	0.11	U
Abdominal Distension	6	0.10	U
Blood Amylase Increased	6	0.10	U
Blood Creatine Phosphokinase Increased	6	0.10	U
Drug Withdrawal Syndrome	6	0.10	U
Dry Eye Nec	6	0.10	U
Extrapyramidal Disorder Nec	6	0.10	U
Galactorrhoea	6	0.10	U
Haematemesis	6	0.10	U
Haemoptysis	6	0.10	U
Hemiplegia	6	0.10	U
Hypercholesterolaemia	6	0.10	U
Hypokalaemia	6	0.10	U
Iron Deficiency Anaemia	6	0.10	U
Leucocytosis Nos	6	0.10	U
Liver Fatty	6	0.10	U
Mental Impairment Nos	6	0.10	U
Migraine Nos	6	0.10	U
Mouth Ulceration	6	0.10	U
Nail Disorder Nos	6	0.10	U
Oliguria	6	0.10	U
Oral Candidiasis	6	0.10	U
Prothrombin Level Decreased	6	0.10	U
Purpura Nos	6	0.10	U
Renal Colic	6	0.10	U
Thirst	6	0.10	U
Tongue Disorder Nos	6	0.10	U

PT	Count of PTs	Percent of Total	Labeled
Urinary Incontinence	6	0.10	U
Vaginal Candidiasis	6	0.10	U
Vertigo Nec	6	0.10	U
Apnoea	5	0.08	U
Atrial Fibrillation	5	0.08	U
Breast Enlargement	5	0.08	U
Cardiovascular Disorder Nos	5	0.08	U
Chest Tightness	5	0.08	U
Cholelithiasis	5	0.08	U
Dermatitis Exfoliative Nos	5	0.08	U
Difficulty In Micturition	5	0.08	U
Drug Effect Increased	5	0.08	U
Emotional Disturbance Nos	5	0.08	U
Gastritis Nos	5	0.08	U
Hiccups	5	0.08	U
Hypoglycaemia Nos	5	0.08	U
Influenza Like Illness	5	0.08	U
Intestinal Obstruction Nos	5	0.08	U
Liver Function Tests Nos Abnormal	5	0.08	U
Lymphadenopathy	5	0.08	U
Menometrorrhagia	5	0.08	U
Movement Disorder Nos	5	0.08	U
Myocardial Infarction	5	0.08	U
Non-Accidental Overdose	5	0.08	U
Overdose Nos	5	0.08	U
Pulmonary Oedema Nos	5	0.08	U
Tongue Discolouration Nos	5	0.08	U
Unexpected Therapeutic Effect	5	0.08	U
Abdominal Pain Upper	4	0.06	U
Aggression	4	0.06	U
Atrioventricular Block Complete	4	0.06	U
Breast Neoplasm Nos	4	0.06	U
Cystitis Nos	4	0.06	U
Dysphonia	4	0.06	U
Erythrocyte Sedimentation Rate Increased	4	0.06	U
Fatigue	4	0.06	U
Haemoglobin Decreased	4	0.06	U
Haemorrhagic Stroke	4	0.06	U

PT	Count of PTs	Percent of Total	Labeled
Hair Disorder Nos	4	0.06	U
Hyperkinetic Syndrome	4	0.06	U
Hyperventilation	4	0.06	U
Idiopathic Thrombocytopenic Purpura	4	0.06	U
Injection Site Oedema	4	0.06	U
Laryngeal Oedema	4	0.06	U
Menstrual Disorder Nos	4	0.06	U
Multi-Organ Failure	4	0.06	U
Neck Stiffness	4	0.06	U
Neoplasm Nos	4	0.06	U
Peptic Ulcer	4	0.06	U
Petechiae	4	0.06	U
Prostatic Disorder Nos	4	0.06	U
Pulsus Bigeminus	4	0.06	U
Rash Erythematous	4	0.06	U
Sinus Bradycardia	4	0.06	U
Suicide Attempt	4	0.06	U
Tenesmus	4	0.06	U
Tolerance Increased	4	0.06	U
Vaginal Haemorrhage	4	0.06	U
Vascular Disorder Nos	4	0.06	U
Vasculitis Nos	4	0.06	U
Acute Circulatory Failure	3	0.05	U
Anti nuclear Factor Positive	3	0.05	U
Aphasia	3	0.05	U
Bipolar I Disorder	3	0.05	U
Blood Electrolytes Nos Abnormal	3	0.05	U
Blood Iron Increased	3	0.05	U
Blood Prolactin Increased	3	0.05	U
Carcinoma Nos	3	0.05	U
Cerebrovascular Accident Nos	3	0.05	U
Cholangitis Nos	3	0.05	U
Complications Of Maternal Exposure To Therapuetic Drugs	3	0.05	U
Coombs Positive Haemolytic Anaemia	3	0.05	U
Deafness Nos	3	0.05	U
Dementia Nos	3	0.05	U
Dyskinesia Nec	3	0.05	U

PT	Count of PTs	Percent of Total	Labeled
Earache	3	0.05	U
Electrocardiogram Qt Prolonged	3	0.05	U
Encephalopathy Nos	3	0.05	U
Erythema Multiforme	3	0.05	U
Gastrointestinal Tract Cancer Nos	3	0.05	U
Glaucoma Nos	3	0.05	U
Growth Retarded	3	0.05	U
Haematocrit Decreased	3	0.05	U
Haemolytic Anaemia Nos	3	0.05	U
Hair Colour Changes	3	0.05	U
Hernia Nos	3	0.05	U
Herpes Zoster	3	0.05	U
Hyperkalaemia	3	0.05	U
Hypoproteinaemia	3	0.05	U
Joint Disorder Nos	3	0.05	U
Lung Disorder Nos	3	0.05	U
Major Depressive Disorder Nos	3	0.05	U
Neck Pain	3	0.05	U
Neurosis Nos	3	0.05	U
Oedema Lower Limb	3	0.05	U
Paraesthesia Circumoral	3	0.05	U
Psoriasis	3	0.05	U
Rectal Disorder Nos	3	0.05	U
Red Blood Cell Count Decreased	3	0.05	U
Renal Failure Acute	3	0.05	U
Skin Odour Abnormal	3	0.05	U
Stupor	3	0.05	U
Tachypnoea	3	0.05	U
Ventricular Extrasystoles	3	0.05	U
Weakness	3	0.05	U
White Blood Cell Count Decreased	3	0.05	U
White Blood Cell Count Increased	3	0.05	U
Accident Nos	2	0.03	U
Albuminuria Present	2	0.03	U
Alkalosis Nos	2	0.03	U
Arthrosis Nos	2	0.03	U
Blindness Nec	2	0.03	U
Blood Glucose Increased	2	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Blood Thromboplastin Decreased	2	0.03	U
Bone Pain	2	0.03	U
Cardiac Failure Nos	2	0.03	U
Cerebral Infarction	2	0.03	U
Cheilitis	2	0.03	U
Coagulation Disorder Nos	2	0.03	U
Congenital Abnormality Nos	2	0.03	U
Coombs Direct Test Positive	2	0.03	U
Coordination Abnormal Nos	2	0.03	U
Creatinine Renal Clearance Decreased	2	0.03	U
Cyanosis Nos	2	0.03	U
Cyst Nos	2	0.03	U
Death	2	0.03	U
Dermatitis Lichenoid	2	0.03	U
Diabetes Mellitus Nos	2	0.03	U
Diarrhoea Haemorrhagic	2	0.03	U
Diplopia	2	0.03	U
Disturbance In Attention Nec	2	0.03	U
Drug Hypersensitivity	2	0.03	U
Dysarthria	2	0.03	U
Dystonia	2	0.03	U
Ejaculation Disorder Nos	2	0.03	U
Enzyme Abnormality Nos	2	0.03	U
Euphoric Mood	2	0.03	U
Eye Disorder Nos	2	0.03	U
Eye Haemorrhage Nec	2	0.03	U
Gastric Ulcer	2	0.03	U
Gastroenteritis Helicobacter	2	0.03	U
Gastrointestinal Necrosis	2	0.03	U
Gingivitis	2	0.03	U
Heart Rate Decreased	2	0.03	U
Hepatitis B Surface Antigen Positive	2	0.03	U
Hepatocellular Damage	2	0.03	U
Hepatorenal Syndrome	2	0.03	U
Hyperlipidaemia Nos	2	0.03	U
Hypernatraemia	2	0.03	U
Hyperuricaemia	2	0.03	U
Hypocalcaemia	2	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Hyponatraemia	2	0.03	U
Hypovolaemia	2	0.03	U
Hypoxia	2	0.03	U
Ileus	2	0.03	U
Injection Site Pain	2	0.03	U
Intracranial Haemorrhage Nos	2	0.03	U
Keratoconjunctivitis	2	0.03	U
Laboratory Test Interference Nos	2	0.03	U
Lacrimal Disorder Nos	2	0.03	U
Laryngitis Nos	2	0.03	U
Liver Tenderness	2	0.03	U
Lymphoma Nos	2	0.03	U
Macrocytic Anaemia Nos	2	0.03	U
Malnutrition Nos	2	0.03	U
Megakaryocytes Increased	2	0.03	U
Mesenteric Occlusion	2	0.03	U
Mucous Membrane Disorder Nos	2	0.03	U
Muscle Spasms	2	0.03	U
Mydriasis	2	0.03	U
Myocardial Ischaemia	2	0.03	U
Myopathy	2	0.03	U
Myositis	2	0.03	U
Nightmare	2	0.03	U
Pallor	2	0.03	U
Pelvic Pain Nos	2	0.03	U
Penile Disorder Nos	2	0.03	U
Peripheral Vascular Disease Nos	2	0.03	U
Premature Baby	2	0.03	U
Prothrombin Level Increased	2	0.03	U
Pulmonary Hypertension Nos	2	0.03	U
Rales	2	0.03	U
Rash Generalised	2	0.03	U
Rash Pustular	2	0.03	U
Renal Impairment Nos	2	0.03	U
Rhonchi	2	0.03	U
Right Ventricular Failure	2	0.03	U
Sinus Tachycardia	2	0.03	U
Skin Disorder Nos	2	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Sleep Disorder Nos	2	0.03	U
Sore Throat Nos	2	0.03	U
Sputum Increased	2	0.03	U
Staphylococcal Infection Nos	2	0.03	U
Stevens Johnson Syndrome	2	0.03	U
Systemic Lupus Erythematosus	2	0.03	U
Tardive Dyskinesia	2	0.03	U
Tendon Disorder Nos	2	0.03	U
Thromboembolism Nos	2	0.03	U
Thrombosis Nos	2	0.03	U
Tooth Discolouration	2	0.03	U
Torticollis	2	0.03	U
Trismus	2	0.03	U
Urinary Retention	2	0.03	U
Vaginitis	2	0.03	U
Ventricular Fibrillation	2	0.03	U
Visual Field Defect Nos	2	0.03	U
White Blood Cell Disorder Nos	2	0.03	U
Abnormal Orgasm (Male)	1	0.02	U
Activated Partial Thromboplastin Time Prolonged	1	0.02	U
Acute Psychosis	1	0.02	U
Adenoma Benign Nos	1	0.02	U
Akathisia	1	0.02	U
Alcohol Intolerance	1	0.02	U
Angina Unstable	1	0.02	U
Anxiety Disorder Nec	1	0.02	U
Appetite Decreased	1	0.02	U
Application Site Reaction Nos	1	0.02	U
Arterial Pressure Nos Decreased	1	0.02	U
Atrial Flutter	1	0.02	U
Atrial Tachycardia	1	0.02	U
Atrioventricular Block First Degree	1	0.02	U
Atrioventricular Block Nos	1	0.02	U
Atrioventricular Block Second Degree	1	0.02	U
Bacterial Infection Nos	1	0.02	U
Balance Impaired Nos	1	0.02	U
Benign Intracranial Hypertension	1	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Bile Duct Obstruction Nos	1	0.02	U
Biliary Colic	1	0.02	U
Bilirubinuria	1	0.02	U
Bladder Stenosis	1	0.02	U
Blood Culture Positive	1	0.02	U
Blood Fibrinogen Increased	1	0.02	U
Blood Follicle Stimulating Hormone Increased	1	0.02	U
Blood Luteinising Hormone Increased	1	0.02	U
Blood Magnesium Decreased	1	0.02	U
Blood Ph Increased	1	0.02	U
Blood Pressure Increased	1	0.02	U
Blood Pressure Systolic Decreased	1	0.02	U
Breast Engorgement	1	0.02	U
Bronchiolitis	1	0.02	U
Bronchitis Nos	1	0.02	U
Bronchospasm Nos	1	0.02	U
Bundle Branch Block Right	1	0.02	U
Caesarean Section	1	0.02	U
Calculus Renal Nos	1	0.02	U
Calculus Urinary	1	0.02	U
Capillary Fragility Increased	1	0.02	U
Cardiospasm	1	0.02	U
Cataract Nec	1	0.02	U
Central Nervous System Neoplasm Nos	1	0.02	U
Cerebral Ischaemia	1	0.02	U
Cerebrovascular Disorder Nos	1	0.02	U
Cervical Disorder Nos	1	0.02	U
Cervical Incompetence	1	0.02	U
Cholangitis Acute Nos	1	0.02	U
Choreoathetosis	1	0.02	U
Coagulation Time Nos Prolonged	1	0.02	U
Colitis Nos	1	0.02	U
Colitis Pseudomembranous	1	0.02	U
Computerised Tomogram Abnormal	1	0.02	U
Conversion Disorder	1	0.02	U
Corneal Lesion Nos	1	0.02	U
Corneal Opacity	1	0.02	U
Coronary Artery Disease Nos	1	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Coronary Artery Occlusion	1	0.02	U
Coronary Artery Surgery	1	0.02	U
Culture Nos Positive	1	0.02	U
Cyanosis Neonatal	1	0.02	U
Decreased Activity	1	0.02	U
Depressed Level Of Consciousness	1	0.02	U
Depression Aggravated	1	0.02	U
Digoxin Toxicity	1	0.02	U
Disorientation	1	0.02	U
Disseminated Intravascular Coagulation	1	0.02	U
Diverticulum Nos	1	0.02	U
Drug Dependence	1	0.02	U
Drug Induced Psychosis	1	0.02	U
Drug Level Nos Below Therapeutic	1	0.02	U
Drug Level Nos Changed	1	0.02	U
Drug Toxicity Nos	1	0.02	U
Ear Infection Nos	1	0.02	U
Eczema Nos	1	0.02	U
Ejection Fraction Abnormal	1	0.02	U
Electrocardiogram Abnormal Nos	1	0.02	U
Electrocardiogram St Segment Elevation	1	0.02	U
Encephalitis Nos	1	0.02	U
Endocrine Disorder Nos	1	0.02	U
Epidermal Necrolysis	1	0.02	U
Extraocular Muscle Paresis	1	0.02	U
Extrasystoles Nos	1	0.02	U
Eye Pain	1	0.02	U
Faeces Discoloured	1	0.02	U
Fibromyalgia Syndrome	1	0.02	U
Flushing	1	0.02	U
Foot Fracture	1	0.02	U
Furuncle (Exc Genital)	1	0.02	U
Gastric Atony	1	0.02	U
Gastric Dilatation	1	0.02	U
Gastric Irritation	1	0.02	U
Gastric Ulcer Perforation	1	0.02	U
Gastroenteritis Nos	1	0.02	U
Gastrointestinal Candidiasis	1	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Gastrointestinal Obstruction Nos	1	0.02	U
Gingival Bleeding	1	0.02	U
Glucose Tolerance Decreased	1	0.02	U
Gout	1	0.02	U
Granuloma Nos	1	0.02	U
Haemodialysis	1	0.02	U
Haemolysis Nos	1	0.02	U
Haemoperitoneum	1	0.02	U
Haemosiderosis	1	0.02	U
Halitosis	1	0.02	U
Hallucination, Visual	1	0.02	U
Hallucinations, Mixed	1	0.02	U
Headache Nos Aggravated	1	0.02	U
Heart Rate Increased	1	0.02	U
Heart Rate Irregular	1	0.02	U
Hepatic Artery Thrombosis	1	0.02	U
Hepatic Cirrhosis Nos	1	0.02	U
Hepatic Necrosis	1	0.02	U
Hepatic Neoplasm Malignant Nos	1	0.02	U
Hepatitis C	1	0.02	U
Hepatomegaly	1	0.02	U
Hepatosplenomegaly	1	0.02	U
Herpes Simplex	1	0.02	U
Hiatus Hernia	1	0.02	U
Hoarseness	1	0.02	U
Hydronephrosis	1	0.02	U
Hypercalcaemia	1	0.02	U
Hyperemesis Gravidarum	1	0.02	U
Hypermagnesaemia	1	0.02	U
Hyperphosphataemia	1	0.02	U
Hypertension Aggravated	1	0.02	U
Hypervolaemia	1	0.02	U
Hypocholesterolaemia	1	0.02	U
Hypophosphataemia	1	0.02	U
Hypotonia	1	0.02	U
Hypoventilation	1	0.02	U
Increased Activity	1	0.02	U
Injection Site Burning	1	0.02	U

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PT	Count of PTs	Percent of Total	Labeled
Injection Site Erythema	1	0.02	U
Injection Site Hypersensitivity	1	0.02	U
Injection Site Urticaria	1	0.02	U
Jaundice Neonatal	1	0.02	U
Joint Swelling	1	0.02	U
Lactation Disorder Nos	1	0.02	U
Left Ventricular Failure	1	0.02	U
Lethargy	1	0.02	U
Lipase Increased	1	0.02	U
Logorrhoea	1	0.02	U
Loin Pain	1	0.02	U
Loss Of Consciousness Nec	1	0.02	U
Masked Facies	1	0.02	U
Megakaryocytes Abnormal	1	0.02	U
Megaloblastic Anaemia Nos	1	0.02	U
Menorrhagia	1	0.02	U
Mental Disorder Nec	1	0.02	U
Metastases To Lymph Nodes	1	0.02	U
Metastatic Neoplasm Nos, Primary Site Unknown	1	0.02	U
Methaemoglobinaemia Nos	1	0.02	U
Micturition Urgency	1	0.02	U
Mouth Haemorrhage	1	0.02	U
Multiple Myeloma	1	0.02	U
Muscle Atrophy	1	0.02	U
Muscle Stiffness	1	0.02	U
Myelodysplastic Syndrome Nos	1	0.02	U
Neck Oedema	1	0.02	U
Necrosis	1	0.02	U
Nephritis Interstitial	1	0.02	U
Nephritis Nos	1	0.02	U
Nephrotic Syndrome	1	0.02	U
Neuralgia Nos	1	0.02	U
No Adverse Effect	1	0.02	U
Nocturia	1	0.02	U
Nystagmus Nos	1	0.02	U
Obstructive Uropathy	1	0.02	U
Oedema Mouth	1	0.02	U

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PT	Count of PTs	Percent of Total	Labeled
Oedema Upper Limb	1	0.02	U
Oesophageal Stenosis	1	0.02	U
Oesophageal Ulcer	1	0.02	U
Oesophageal Ulcer Haemorrhage	1	0.02	U
Operation Nos	1	0.02	U
Opisthotonus	1	0.02	U
Oral Mucosal Blistering	1	0.02	U
Otitis Media Nos	1	0.02	U
Pain In Limb	1	0.02	U
Pancreatitis Acute On Chronic	1	0.02	U
Pancreatitis Necrotising	1	0.02	U
Paralysis Nos	1	0.02	U
Peptic Ulcer Haemorrhage	1	0.02	U
Peptic Ulcer Perforation	1	0.02	U
Peptic Ulcer Reactivated	1	0.02	U
Pericardial Effusion	1	0.02	U
Peristalsis Visible	1	0.02	U
Pharyngeal Disorder Nos	1	0.02	U
Pharyngeal Oedema	1	0.02	U
Photophobia	1	0.02	U
Platelet Abnormalities Nos	1	0.02	U
Pleural Effusion	1	0.02	U
Pneumonitis Aspiration	1	0.02	U
Polyarthralgia	1	0.02	U
Polyp Nos	1	0.02	U
Polyuria	1	0.02	U
Postural Hypotension	1	0.02	U
Pregnancy Nos	1	0.02	U
Priapism	1	0.02	U
Prostate Cancer Nos	1	0.02	U
Pulmonary Embolism	1	0.02	U
Pulmonary Fibrosis	1	0.02	U
Pyelonephritis Nos	1	0.02	U
Pyuria	1	0.02	U
Rash Macular	1	0.02	U
Rash Pruritic	1	0.02	U
Red Eye	1	0.02	U
Refractive Errors Nos	1	0.02	U

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PT	Count of PTs	Percent of Total	Labeled
Respiratory Arrest (Exc Neonatal)	1	0.02	U
Respiratory Distress	1	0.02	U
Respiratory Failure (Exc Neonatal)	1	0.02	U
Scrotal Infection Nos	1	0.02	U
Scrotal Oedema	1	0.02	U
Sialoadenitis Nos	1	0.02	U
Sinusitis Nos	1	0.02	U
Skin Atrophy	1	0.02	U
Spinal Disorder Nos	1	0.02	U
Streptococcal Infection Nos	1	0.02	U
Stridor	1	0.02	U
Supraventricular Tachycardia	1	0.02	U
Testicular Failure Nec	1	0.02	U
Throat Tightness	1	0.02	U
Thrombotic Thrombocytopenic Purpura	1	0.02	U
Thyroid Disorder Nos	1	0.02	U
Tongue Coated	1	0.02	U
Tooth Caries Nos	1	0.02	U
Tooth Disorder Nos	1	0.02	U
Torsade De Pointes	1	0.02	U
Tunnel Vision	1	0.02	U
Ultrasound Scan Nos Abnormal	1	0.02	U
Urinary Tract Disorder Nos	1	0.02	U
Ventricular Asystole	1	0.02	U
Viral Infection Nos	1	0.02	U
Vision Blurred	1	0.02	U
Visual Disturbance Nos	1	0.02	U
Vitreous Disorder Nos	1	0.02	U
Vulvovaginal Disorder Nos	1	0.02	U
Wandering Around	1	0.02	U
Yellow Skin	1	0.02	U

Adverse Event Reporting System (AERS)

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 08/10/2000 - 01:07 pm

Search Criteria:

Product Name(s): AXID (T)
NIZATIDINE (A)

Manufacturer Type Sender of ISR

Search Type: CASE
Search for reactions listed: ANY
FDA Rcvd. Date: From:
Reporter Domestic: YES
Reporter First Name:
Null Values for Country
Female:
Age Range: From
MedWatch Source Study
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
PA Summary ISR
Include Deactived ISRs
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #:
FDA Rcvd. Date: To: 03/31/2000
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products
Mfr. Control #:
Sort in Descending Order
Reporter Last Name
Reporter State
Male
Null Gender Value
Age Range: YEAR
MedWatch Source Consumer
Periodic ISR
5 Day ISR
Follow-up
Serious Outcome
Event Start Date:
ReC

Non-Excluded Product(s) for Selected Active Ingredient(s):

AXID (T)
ACINON (V)
ACIX (NIZATIDINE) (V)
NIZATIDINE (V)
OLANZAPINE (V)
AXID AR (T)
ACINON (NIZATIDINE) (V)
AXID AR (V)
NIZAX (V)
PANAXID (V)
NIZATIDINE (T)
ACINON 150 (NIZATIDINE) (V)
COVERSYL (PERINDOPRIL) (V)
NIZAX (NIZATIDINE) (V)
TAZAC (V)
. (V)
ACINON(NIZATIDINE) (V)
NIZATIDEINE (V)
NIZAX CAPSULES (V)

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Dermatitis Nos	414	12.05	U
Drug Ineffective	361	10.51	U
Urticaria Nos	214	6.23	U
Diarrhoea Nos	193	5.62	U
Nausea	182	5.30	U
Abdominal Pain Nos	179	5.21	U
Headache Nos	150	4.37	U
Pruritus	146	4.25	U
Dyspnoea Nos	129	3.75	U
Dizziness (Exc Vertigo)	120	3.49	U
Dyspepsia	106	3.08	U
Vomiting Nos	104	3.03	U
Hepatic Function Abnormal Nos	85	2.47	U
Confusion	84	2.44	U
Asthenia	72	2.10	U
Chest Pain	66	1.92	U
Sedation	66	1.92	U
Pyrexia	64	1.86	U
Hypersensitivity Nos	63	1.83	U
Insomnia Nec	63	1.83	U
Anaphylactic Reaction	62	1.80	U
Face Oedema	58	1.69	U
Flatulence	56	1.63	U
Thrombocytopenia	50	1.46	U
Sweating Increased	49	1.43	U
Alopecia	48	1.40	U
Constipation	48	1.40	U
Pain Nos	45	1.31	U
Tachycardia Nos	45	1.31	U
Paraesthesia Nec	42	1.22	U
Abnormal Dreams	40	1.16	U
Hepatitis Nos	40	1.16	U
Nervousness	40	1.16	U
Condition Aggravated	39	1.14	U
Vasodilatation	39	1.14	U
Jaundice Nos	37	1.08	U
Taste Disturbance	37	1.08	U
Drug Interaction Nos	34	0.99	U

PT	Count of PTs	Percent of Total	Labeled
Amblyopia Nos	32	0.93	U
Gastrointestinal Haemorrhage Nos	32	0.93	U
Gynaecomastia	30	0.87	U
Palpitations	30	0.87	U
Malaise	29	0.84	U
Hallucination Nos	28	0.81	U
Depression Nec	27	0.79	U
Impotence	26	0.76	U
Agitation	25	0.73	U
Arthralgia	25	0.73	U
Hypotension	25	0.73	U
Pharyngitis Nos	25	0.73	U
Aspartate Aminotransferase Increased	24	0.70	U
Oedema Nos	24	0.70	U
Oedema Peripheral	24	0.70	U
Syncope	24	0.70	U
Asthma Nos	23	0.67	U
Dry Mouth	23	0.67	U
Hypertension Nos	22	0.64	U
Blood Bilirubin Increased	21	0.61	U
Myalgia	20	0.58	U
Thinking Abnormal Nec	19	0.55	U
Stomatitis	18	0.52	U
Alanine Aminotransferase Increased	17	0.49	U
Anaemia Nos	17	0.49	U
Anxiety Nec	17	0.49	U
Back Pain	17	0.49	U
Faecal Abnormality Nos	17	0.49	U
Tremor Nec	17	0.49	U
Unevaluable Reaction	17	0.49	U
Drug Level Nos Above Therapeutic	16	0.47	U
Leucopenia Nos	16	0.47	U
Rhinitis Nos	16	0.47	U
Laryngospasm	15	0.44	U
Overdose Nos	15	0.44	U
Accident Nos	14	0.41	U
Amnesia Nec	14	0.41	U
Anorexia	14	0.41	U

PT	Count of PTs	Percent of Total	Labeled
Cough	14	0.41	U
Gastrointestinal Disorder Nos	14	0.41	U
Tongue Oedema	14	0.41	U
Weight Decreased	14	0.41	U
Urinary Frequency	13	0.38	U
Urine Abnormal Nos	13	0.38	U
Angioneurotic Oedema	12	0.35	U
Blood Alkaline Phosphatase Nos Increased	12	0.35	U
Breast Pain	12	0.35	U
Dysphagia	12	0.35	U
Eructation	12	0.35	U
Glossitis	12	0.35	U
Tinnitus	12	0.35	U
Dermatitis Bullous	11	0.32	U
Ecchymosis	11	0.32	U
Leucocytosis Nos	11	0.32	U
Photosensitivity Reaction Nos	11	0.32	U
Unexpected Therapeutic Effect	11	0.32	U
Urinary Retention	11	0.32	U
Weight Increased	11	0.32	U
Dysuria	10	0.29	U
Emotional Disturbance Nos	10	0.29	U
Hypertonia	10	0.29	U
Hypoglycaemia Nos	10	0.29	U
Idiopathic Thrombocytopenic Purpura	10	0.29	U
Infection Nos	10	0.29	U
Mouth Ulceration	10	0.29	U
Pancreatitis Nos	10	0.29	U
Rash Maculo-Papular	10	0.29	U
Arrhythmia Nos	9	0.26	U
Epistaxis	9	0.26	U
Gamma-Glutamyltransferase Increased	9	0.26	U
Haematuria Present	9	0.26	U
Hypoaesthesia	9	0.26	U
Jaundice Cholestatic	9	0.26	U
Libido Decreased	9	0.26	U
Melaena	9	0.26	U
Pneumonia Nos	9	0.26	U

PT	Count of PTs	Percent of Total	Labeled
Unintended Pregnancy	9	0.26	U
Arthritis Nos	8	0.23	U
Bone Marrow Depression Nos	8	0.23	U
Dehydration	8	0.23	U
Erythema Multiforme	8	0.23	U
Euphoric Mood	8	0.23	U
Eye Pain	8	0.23	U
Neck Pain	8	0.23	U
Petechiae	8	0.23	U
Purpura Nos	8	0.23	U
Sepsis Nos	8	0.23	U
Urinary Tract Infection Nos	8	0.23	U
Vasculitis Nos	8	0.23	U
Vision Abnormal Nec	8	0.23	U
Abdominal Distension	7	0.20	U
Accidental Overdose (Therapeutic Agent)	7	0.20	U
Ataxia Nec	7	0.20	U
Cardiac Arrest	7	0.20	U
Convulsions Nos	7	0.20	U
Depersonalisation	7	0.20	U
Influenza Like Illness	7	0.20	U
Myasthenic Syndrome	7	0.20	U
Oesophagitis	7	0.20	U
Prothrombin Level Decreased	7	0.20	U
Rigors	7	0.20	U
Sleep Disorder Nos	7	0.20	U
Apnoea	6	0.17	U
Arthrosis Nos	6	0.17	U
Blood Lactate Dehydrogenase Increased	6	0.17	U
Bradycardia Nos	6	0.17	U
Cyanosis Nos	6	0.17	U
Dermatitis Exfoliative Nos	6	0.17	U
Galactorrhoea	6	0.17	U
Gastrointestinal Tract Cancer Nos	6	0.17	U
Joint Disorder Nos	6	0.17	U
Laboratory Test Abnormal Nos	6	0.17	U
Laboratory Test Interference Nos	6	0.17	U
Laryngeal Oedema	6	0.17	U

PT	Count of PTs	Percent of Total	Labeled
Migraine Nos	6	0.17	U
Myocardial Infarction	6	0.17	U
Non-Accidental Overdose	6	0.17	U
Parosmia	6	0.17	U
Stupor	6	0.17	U
Acne Nos	5	0.15	U
Blood Creatinine Increased	5	0.15	U
Calculus Renal Nos	5	0.15	U
Delirium	5	0.15	U
Dry Eye Nec	5	0.15	U
Eosinophilia (Exc Pulmonary)	5	0.15	U
Extrapyramidal Disorder Nec	5	0.15	U
Eye Disorder Nos	5	0.15	U
Gait Abnormal Nos	5	0.15	U
Gastroenteritis Nos	5	0.15	U
Gout	5	0.15	U
Hyperglycaemia Nos	5	0.15	U
Lymphadenopathy	5	0.15	U
Muscle Twitching	5	0.15	U
Nocturia	5	0.15	U
Polyuria	5	0.15	U
Tongue Discolouration Nos	5	0.15	U
Antinuclear Factor Positive	4	0.12	U
Blood Urea Increased	4	0.12	U
Breast Enlargement	4	0.12	U
Cerebrovascular Accident Nos	4	0.12	U
Cholelithiasis	4	0.12	U
Coordination Abnormal Nos	4	0.12	U
Delusion Nos	4	0.12	U
Drug Level Nos Below Therapeutic	4	0.12	U
Duodenal Ulcer Perforation	4	0.12	U
Fall	4	0.12	U
Gastric Ulcer Haemorrhage	4	0.12	U
Haematemesis	4	0.12	U
Hyperthyroidism	4	0.12	U
Lung Disorder Nos	4	0.12	U
Pancytopenia	4	0.12	U
Paraesthesia Circumoral	4	0.12	U

FDA - Adverse Event Reporting System (AERS)
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PT	Count of PTs	Percent of Total	Labeled
Peripheral Neuropathy Nec	4	0.12	U
Premature Labour	4	0.12	U
Renal Failure Acute	4	0.12	U
Right Ventricular Failure	4	0.12	U
Skin Odour Abnormal	4	0.12	U
Speech Disorder Nec	4	0.12	U
Taste Loss	4	0.12	U
Urinary Incontinence	4	0.12	U
Ventricular Extrasystoles	4	0.12	U
Vertigo Nec	4	0.12	U
Acute Circulatory Failure	3	0.09	U
Blood Amylase Increased	3	0.09	U
Blood Dyscrasia Nos	3	0.09	U
Cardiovascular Disorder Nos	3	0.09	U
Central Nervous System Depression Nos	3	0.09	U
Coagulation Time Nos Prolonged	3	0.09	U
Complications Of Maternal Exposure To Therapuetic Drugs	3	0.09	U
Conjunctivitis Nec	3	0.09	U
Difficulty In Micturition	3	0.09	U
Drug Dependence	3	0.09	U
Drug Effect Increased	3	0.09	U
Drug Maladministration	3	0.09	U
Drug Withdrawal Syndrome	3	0.09	U
Dry Skin	3	0.09	U
Epidermal Necrolysis	3	0.09	U
Erythrocyte Sedimentation Rate Increased	3	0.09	U
Fatigue	3	0.09	U
Gastric Ulcer	3	0.09	U
Haematocrit Decreased	3	0.09	U
Haemoglobin Decreased	3	0.09	U
Haemoptysis	3	0.09	U
Haemorrhage Nos	3	0.09	U
Hair Disorder Nos	3	0.09	U
Hemiplegia	3	0.09	U
Hip Fracture	3	0.09	U
Hostility	3	0.09	U
Hyperkalaemia	3	0.09	U

PT	Count of PTs	Percent of Total	Labeled
Hyperkinetic Syndrome	3	0.09	U
Hyperuricaemia	3	0.09	U
Hyperventilation	3	0.09	U
Hypokalaemia	3	0.09	U
Intestinal Obstruction Nos	3	0.09	U
Iron Deficiency Anaemia	3	0.09	U
Lethargy	3	0.09	U
Liver Fatty	3	0.09	U
Menometrorrhagia	3	0.09	U
Micturition Urgency	3	0.09	U
Mucous Membrane Disorder Nos	3	0.09	U
Muscle Cramps	3	0.09	U
Paranoia	3	0.09	U
Peptic Ulcer	3	0.09	U
Platelet Count Decreased	3	0.09	U
Prostatic Disorder Nos	3	0.09	U
Renal Colic	3	0.09	U
Renal Failure Nos	3	0.09	U
Renal Impairment Nos	3	0.09	U
Skin Disorder Nos	3	0.09	U
Supraventricular Tachycardia	3	0.09	U
Tardive Dyskinesia	3	0.09	U
Tooth Disorder Nos	3	0.09	U
Aggression	2	0.06	U
Agranulocytosis	2	0.06	U
Akathisia	2	0.06	U
Albuminuria Present	2	0.06	U
Angina Pectoris	2	0.06	U
Apathy	2	0.06	U
Appetite Increased	2	0.06	U
Atrial Fibrillation	2	0.06	U
Atrioventricular Block Complete	2	0.06	U
Bacterial Infection Nos	2	0.06	U
Balanitis Nos	2	0.06	U
Blindness Nec	2	0.06	U
Blood Creatine Phosphokinase Increased	2	0.06	U
Blood Prolactin Increased	2	0.06	U
Carcinoma Nos	2	0.06	U

PT	Count of PTs	Percent of Total	Labeled
Cardiospasm	2	0.06	U
Cellulitis	2	0.06	U
Cerebral Ischaemia	2	0.06	U
Coagulation Disorder Nos	2	0.06	U
Colitis Nos	2	0.06	U
Coma Nec	2	0.06	U
Death	2	0.06	U
Diplopia	2	0.06	U
Dysphonia	2	0.06	U
Ear Disorder Nos	2	0.06	U
Ejaculation Disorder Nos	2	0.06	U
Electrocardiogram Abnormal Nos	2	0.06	U
Encephalopathy Nos	2	0.06	U
Enzyme Abnormality Nos	2	0.06	U
Gastritis Nos	2	0.06	U
Glomerulonephritis Nos	2	0.06	U
Hangover (Exc Alcohol)	2	0.06	U
Hepatic Failure	2	0.06	U
Hepatocellular Damage	2	0.06	U
Hepatomegaly	2	0.06	U
Hernia Nos	2	0.06	U
Hypercholesterolaemia	2	0.06	U
Hyperlipidaemia Nos	2	0.06	U
Hypoproteinaemia	2	0.06	U
Inappropriate Adh Secretion	2	0.06	U
Injection Site Reaction Nos	2	0.06	U
Lacrimal Disorder Nos	2	0.06	U
Liver Function Tests Nos Abnormal	2	0.06	U
Liver Tenderness	2	0.06	U
Lung Cancer Stage Unspecified (Exc Metastatic Tumours To Lung)	2	0.06	U
Macrocytic Anaemia Nos	2	0.06	U
Mouth Haemorrhage	2	0.06	U
Myoclonic Jerks	2	0.06	U
Pathological Fracture	2	0.06	U
Penile Disorder Nos	2	0.06	U
Personality Disorder Nos	2	0.06	U
Photophobia	2	0.06	U

PT	Count of PTs	Percent of Total	Labeled
Postural Hypotension	2	0.06	U
Prothrombin Level Increased	2	0.06	U
Psychotic Disorder Nos	2	0.06	U
Pulmonary Oedema Nos	2	0.06	U
Pyloric Stenosis Nos	2	0.06	U
Rectal Disorder Nos	2	0.06	U
Salivary Gland Enlargement Nos	2	0.06	U
Serum Sickness	2	0.06	U
Skin Carcinoma Nos	2	0.06	U
Skin Discolouration	2	0.06	U
Systemic Lupus Erythematosus	2	0.06	U
Thrombocythaemia	2	0.06	U
Tongue Disorder Nos	2	0.06	U
Urinary Tract Disorder Nos	2	0.06	U
Uterine Haemorrhage	2	0.06	U
Vaginal Candidiasis	2	0.06	U
Vaginal Haemorrhage	2	0.06	U
Ventricular Tachycardia	2	0.06	U
Abdominal Pain Upper	1	0.03	U
Abortion Nos	1	0.03	U
Abscess Nos	1	0.03	U
Adrenal Insufficiency Nos	1	0.03	U
Adult Respiratory Distress Syndrome	1	0.03	U
Agitation Aggravated	1	0.03	U
Alcohol Intolerance	1	0.03	U
Anaphylactic Shock	1	0.03	U
Anaphylactoid Reaction	1	0.03	U
Antepartum Haemorrhage	1	0.03	U
Aplastic Anaemia	1	0.03	U
Arteritis Nos	1	0.03	U
Ascites	1	0.03	U
Aspermia	1	0.03	U
Atrioventricular Block Nos	1	0.03	U
Balance Impaired Nos	1	0.03	U
Bleeding Time Prolonged	1	0.03	U
Blood Sodium Decreased	1	0.03	U
Bone Disorder Nos	1	0.03	U
Breast Neoplasm Nos	1	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Cardiac Failure Congestive	1	0.03	U
Cardiac Failure Nos	1	0.03	U
Cardio-Respiratory Arrest	1	0.03	U
Cardiomyopathy Nos	1	0.03	U
Cataract Nec	1	0.03	U
Cerebral Infarction	1	0.03	U
Cerebrovascular Disorder Nos	1	0.03	U
Cheilitis	1	0.03	U
Chest Pressure Sensation	1	0.03	U
Cholangitis Acute Nos	1	0.03	U
Cholangitis Sclerosing	1	0.03	U
Cholecystitis Nos	1	0.03	U
Chondrodystrophy	1	0.03	U
Choreoathetosis	1	0.03	U
Congenital Abnormality Nos	1	0.03	U
Corneal Opacity	1	0.03	U
Coronary Artery Occlusion	1	0.03	U
Creatinine Renal Clearance Decreased	1	0.03	U
Cystitis Nos	1	0.03	U
Deafness Nos	1	0.03	U
Deafness Transitory	1	0.03	U
Depression Aggravated	1	0.03	U
Dermatitis Contact	1	0.03	U
Diabetic Complication Nos	1	0.03	U
Diarrhoea Haemorrhagic	1	0.03	U
Distress	1	0.03	U
Duodenal Ulcer Haemorrhage	1	0.03	U
Duodenitis	1	0.03	U
Dyskinesia Nec	1	0.03	U
Dysmenorrhoea	1	0.03	U
Dystonia	1	0.03	U
Earache	1	0.03	U
Eclampsia	1	0.03	U
Electrocardiogram St Segment Elevation	1	0.03	U
Erythema Nodosum	1	0.03	U
Faecal Incontinence	1	0.03	U
Feeling Abnormal	1	0.03	U
Feeling Hot	1	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Fibrocystic Breast Disease	1	0.03	U
Fixed Eruption	1	0.03	U
Fungal Infection Nos	1	0.03	U
Furuncle (Exc Genital)	1	0.03	U
Gastric Ulcer Perforation	1	0.03	U
Genital Oedema Female	1	0.03	U
Gestational Diabetes	1	0.03	U
Gingival Bleeding	1	0.03	U
Glaucoma Nos	1	0.03	U
Granuloma Nos	1	0.03	U
Haematoma Nos	1	0.03	U
Haemolytic Anaemia Nos	1	0.03	U
Haemorrhagic Stroke	1	0.03	U
Hallucination, Tactile	1	0.03	U
Hallucination, Visual	1	0.03	U
Head Injury	1	0.03	U
Hepatic Cirrhosis Nos	1	0.03	U
Hepatic Necrosis	1	0.03	U
Hypercalcaemia	1	0.03	U
Hypokinesia	1	0.03	U
Hyponatraemia	1	0.03	U
Hyporeflexia	1	0.03	U
Hypothermia	1	0.03	U
Hypothyroidism	1	0.03	U
Hypoventilation	1	0.03	U
Hypovolaemia	1	0.03	U
Ileus	1	0.03	U
Le Test Abnormal	1	0.03	U
Leukocytoclastic Vasculitis	1	0.03	U
Lymphoma Nos	1	0.03	U
Major Depressive Disorder Nos	1	0.03	U
Mastitis	1	0.03	U
Megaloblastic Anaemia Nos	1	0.03	U
Miosis	1	0.03	U
Mucosal Erosion Nos	1	0.03	U
Myelocytic Maturation Arrest	1	0.03	U
Myeloproliferative Disorder Nos	1	0.03	U
Myocardial Ischaemia	1	0.03	U

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PT	Count of PTs	Percent of Total	Labeled
Nail Abnormality Nos	1	0.03	U
Nail Disorder Nos	1	0.03	U
Neoplasm Nos	1	0.03	U
Oesophageal Haemorrhage	1	0.03	U
Oesophageal Stenosis	1	0.03	U
Oesophageal Ulcer	1	0.03	U
Oliguria	1	0.03	U
Oral Candidiasis	1	0.03	U
Otitis Media Nos	1	0.03	U
Pain In Limb	1	0.03	U
Pancreatic Disorder Nos	1	0.03	U
Paralysis Nos	1	0.03	U
Parkinsonism	1	0.03	U
Parotid Gland Enlargement	1	0.03	U
Pelvic Pain Nos	1	0.03	U
Pericarditis Nos	1	0.03	U
Personality Change	1	0.03	U
Pleural Effusion	1	0.03	U
Pneumonitis Nos	1	0.03	U
Porphyria Nos	1	0.03	U
Proctitis Nos	1	0.03	U
Prostatic Specific Antigen Increased	1	0.03	U
Psoriasis	1	0.03	U
Pulmonary Embolism	1	0.03	U
Pulmonary Fibrosis	1	0.03	U
Pulsus Bigeminus	1	0.03	U
Pyelonephritis Nos	1	0.03	U
Pyuria	1	0.03	U
Rash Erythematous	1	0.03	U
Rash Macular	1	0.03	U
Renal Cyst Nos	1	0.03	U
Respiratory Depression	1	0.03	U
Respiratory Disorder Nos	1	0.03	U
Respiratory Rate Decreased	1	0.03	U
Retching	1	0.03	U
Retinal Degeneration*	1	0.03	U
Retinal Disorder Nos	1	0.03	U
Rheumatoid Arthritis	1	0.03	U

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PT	Count of PTs	Percent of Total	Labeled
Sarcoidosis Nos	1	0.03	U
Sarcoma Nos	1	0.03	U
Schizophrenia Nos	1	0.03	U
Seborrhoea	1	0.03	U
Sinusitis Nos	1	0.03	U
Skin Necrosis	1	0.03	U
Skin Neoplasm Nos	1	0.03	U
Sputum Increased	1	0.03	U
Stevens Johnson Syndrome	1	0.03	U
Stillbirth	1	0.03	U
Stress Symptoms	1	0.03	U
Stridor	1	0.03	U
Sudden Death Unexplained	1	0.03	U
Swelling Nos	1	0.03	U
Tachypnoea	1	0.03	U
Testicular Disorder Nos	1	0.03	U
Thirst	1	0.03	U
Tooth Caries Nos	1	0.03	U
Tooth Discolouration	1	0.03	U
Trismus	1	0.03	U
Urate Urine Increased	1	0.03	U
Uterine Disorder Nos	1	0.03	U
Uveitis Nos	1	0.03	U
Vaginitis	1	0.03	U
Vascular Disorder Nos	1	0.03	U
Vascular Purpura	1	0.03	U
Venous Pressure Jugular Increased	1	0.03	U
Ventricular Arrhythmia Nos	1	0.03	U
Visual Field Defect Nos	1	0.03	U
Vulvovaginitis Nos	1	0.03	U
Weakness	1	0.03	U
White Blood Cell Disorder Nos	1	0.03	U

dverse Ev...t Reporting System (AER

Standard Report
Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 08/10/2000 - 01:08 pm

Search Criteria:

Product Name(s): AXID (T)
NIZATIDINE (A)

Manufacturer Type: Sender of ISR
Search Type: CASE
Search for reactions listed: ANY
FDA Revd. Date: From:
Reporter Domestic: YES
Reporter First Name:
Full Values for Country
Female:
Age Range: From
MedWatch Source Study
MedWatch Source Health Professional:
Expedited (15-Day) ISR:
RA Summary ISR
Include Deactived ISRs
Non-Serious Outcome:
Event End Date:
OTC Products Only:

Include Concomitant Products:
ISR/Case #:
FDA Revd. Date: To: 03/31/2000
Reporter Foreign:
Reporter City:
Patient ID:
Gender Unknown:
Age Range: To:
MedWatch Source Literature
Direct ISR:
10 Day ISR:
Initial:
Processed ISRs/Cases Only: YES
ISRs with No Outcome Reported:
DeC:

Include Combination Products
Mfr. Control #:
Sort in Descending Order
Reporter Last Name
Reporter State
Male
Null Gender Value
Age Range: YEAR
MedWatch Source Consumer
Periodic ISR
5 Day ISR
Follow-up
Serious Outcome
Event Start Date:
ReC

Non-Excluded Product(s) for Selected Active Ingredient(s):

AXID (T)
ACINON (V)
ACIX (NIZATIDINE) (V)
NIZATIDINE (V)
OLANZAPINE (V)
AXID AR (T)
ACINON (NIZATIDINE) (V)
AXID AR (V)
NIZAX (V)
PANAXID (V)
NIZATIDINE (T)
ACINON 150 (NIZATIDINE) (V)
COVERSYL (PERINDOPRIL) (V)
NIZAX (NIZATIDINE) (V)
TAZAC (V)
(V)
ACINON(NIZATIDINE) (V)
NIZATIDEINE (V)
NIZAX CAPSULES (V)

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1988	1	1	0	0	0	0	0	0	0
	3	46	18	6	14	0	3	0	0
	4	139	10	3	10	0	0	0	0
	Subtotal	186	28	9	24	0	3	0	0
1989	1	134	25	2	24	0	0	0	0
	2	96	12	1	11	0	0	0	0
	3	129	25	0	25	0	0	0	0
	4	174	12	2	12	0	1	0	0
	Subtotal	533	74	5	72	0	1	0	0
1990	1	118	17	1	16	0	0	0	0
	2	115	6	0	6	0	0	0	0
	3	84	11	0	11	0	0	0	0
	4	78	8	2	8	1	0	0	0
	Subtotal	395	42	3	41	1	0	0	0
1991	1	72	8	2	7	0	0	0	0
	2	84	13	0	13	0	0	0	0
	3	16	5	0	5	0	0	0	0
	4	7	5	4	2	0	0	0	0
	Subtotal	179	31	6	27	0	0	0	0
1992	1	5	3	0	3	0	0	0	0
	2	345	22	1	20	0	1	0	0
	3	7	3	1	2	0	0	0	0
	4	3	3	1	2	0	0	0	0
	Subtotal	360	31	3	27	0	1	0	0
1993	1	3	2	0	2	0	0	0	0
	2	305	12	2	11	0	0	0	0
	3	9	6	0	2	0	0	0	0
	4	6	4	0	3	1	1	0	1
	Subtotal	323	24	2	18	1	1	0	1
1994	1	11	10	0	4	3	0	0	0
	2	199	39	1	34	2	0	0	1
	3	9	6	1	6	3	1	0	3
	4	6	3	0	3	0	0	0	0
	Subtotal	225	58	2	47	8	1	0	4

Search Criteria Name: CORKENA Search submitted on: 08-10-2000 12:59:09
Product/Group Name: NIZATIDINE (A)
Reaction/Group Name:
Search Case Count:3436

Date - Time: 08/10/2000 - 01:08 pm
Run by: CORKENA

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1995	1	13	8	1	4	0	0	0	0
	2	11	9	0	3	1	0	0	1
	3	214	26	1	16	2	1	0	1
	4	15	7	0	2	0	0	0	2
	Subtotal	253	50	2	25	3	1	0	4
1996	1	9	5	0	3	1	0	0	2
	2	155	12	0	6	0	0	0	2
	3	98	4	1	1	0	0	0	5
	4	241	6	0	3	0	0	0	0
	Subtotal	503	27	1	13	1	0	0	9
1997	1	142	7	0	5	1	1	0	2
	2	260	11	1	6	2	0	0	0
	4	9	8	1	4	1	0	2	0
	Subtotal	411	26	2	15	4	1	2	2
1998	1	2	2	0	2	0	0	0	0
	2	10	7	0	6	0	0	0	1
	3	3	3	0	1	0	0	0	0
	4	3	3	1	2	1	0	0	0
	Subtotal	18	15	1	11	1	0	0	1
1999	1	14	2	0	2	0	0	0	0
	2	25	3	0	3	0	0	0	0
	3	4	1	0	0	0	0	0	1
	4	4	3	1	1	1	0	0	0
	Subtotal	47	9	1	6	1	0	0	1
2000	1	3	2	0	2	0	0	0	0
	Subtotal	3	2	0	2	0	0	0	0
Total		3436	417	37	328	20	9	2	22

APPEARS THIS WAY
ON ORIGINAL

Search Criteria Name: CORKENA Search submitted on: 08-10-2000 12:59:09
Product/Group Name: NIZATIDINE (A)
Reaction/Group Name:
Search Case Count3436

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Date - Time: 08/10/2000 - 01:08 pm
Run by: CORKENA

Adverse Event Reporting System (AERS)

Standard Report

Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 05/31/2000 - 10:30 am

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Search Criteria:

Product Name(s):

- RANITIDINE (A)
- RANITIDINE BISMUTH CITRATE (A)
- RANITIDINE HYDROCHLORIDE (A)
- ZANTAC (RANITIDINE) (V)
- ZANTAC (T)
- ZANTAC (V)
- ZANTAC 75 OTC TABLET (V)
- ZANTAC 300MG (V)
- ZANTAC 50 MG (V)
- ZANTAC 75 OTC TABLET (V)
- ZANTAC-75 WARNER-LAMBERT (RANITIDINE) (V)

Manufacturer Type: Sender of ISR

Search Type: CASE	**Include Concomitant Products:**	**Include Combination Products**
Search for reactions listed: ANY	**ISR/Case #:**	**Mfr. Control #:**
FDA Recvd. Date: From:	**FDA Recvd. Date: To: 03/31/2000**	**Sort in Descending Order**
Reporter Domestic: YES	**Reporter Foreign:**	**Reporter Last Name**
Reporter First Name:	**Reporter City:**	**Reporter State**
Null Values for Country	**Patient ID:**	**Male**
Female:	**Gender Unknown:**	**Null Gender Value**
Age Range: From	**Age Range: To:**	**Age Range: YEAR**
MedWatch Source Study	**MedWatch Source Literature**	**MedWatch Source Consumer**
MedWatch Source Health Professional:	**Direct ISR:**	**Periodic ISR**
Expedited (15-Day) ISR:	**10 Day ISR:**	**5 Day ISR**
RA Summary ISR	**Initial:**	**Follow-up**
Include Deactived ISRs	**Processed ISRs/Cases Only: YES**	**Serious Outcome**
Non-Serious Outcome:	**ISRs with No Outcome Reported:**	**Event Start Date:**
Event End Date:	**DeC:**	**ReC**
OTC Products Only:		

dverse Ev..t Reporting System (AER

Standard Report

Cases by Year and Quarter

Run by: ANN CORKEN Date - Time: 05/31/2000 - 10:30 am

Non-Excluded Product(s) for Selected Active Ingredient(s):

RANITIDINE (T)
RANITIDINE HCL (T)
RANITIDINE HYDROCHLORIDE (T)
TRITEC (T)
ZANTAC (T)
ZANTAC 150 (T)
ZANTAC 300 (T)
ZANTAC 75 (T)
AZANTAC (V)
AZANTAC 150 MG (V)
AZANTAC (RANITIDINE HCL) (V)
AZANTAC (RANITIDINE) (V)
AZANTAC (RANITIDINE) UNKNOWN (V)
AZANTAC / 150 (V)
AZANTAC 150 MG (V)
AZANTAC INJECTABLE SOLUTION (V)
AZANTAC\150 (V)
CALCIUM CARBONATE (V)
CEFTAZIDINE (MODACINE) (V)
GENERIC RANITADINE (V)
GENERIC RANITIDINE (150 MG OR 300 MG) (V)
GENEVA GENERICS (V)
RANI 2(RANITIDINE HCL) (V)
RANIDIL (V)
RANIPLEX (V)
RANIPLEX (RANITIDINE HCL) (V)
RANIPLEX (RANITIDINE) (V)
RANITIC (RANITIDINE) 150 MG (V)
RANITIDIN (RANITIDINE) (V)
RANITIDIN SOLUTION FOR INJECTION (V)
RANITIDIN TABLETS (V)
RANITIDINA (RANITIDINE) (V)
RANITIDINE (V)
RANITIDINE /50 MG GENEVA (V)
RANITIDINE 150MG (V)
RANITIDINE 300 MG BID (V)
RANITIDINE 300MG (V)
RANITIDINE HYDROCHLORIDE (V)
RANITIDINE HYDROCHLORIDE (AZANTAC) SOLUTION FOR INJECTION (V)
RANITIDINE HYDROCHLORIDE (FORMULATION UNKNOWN) (V)
RANITIDINE HYDROCHLORIDE (RANITIDINE) TABLET (V)
RANITIDINE TABLET (RANITIDINE HYDROCHLORIDE) (V)
RANITIDINE TABLETS USP (V)
RANITIDINE TABLETS, 150 MG APOTEX LABEL (V)
RANITIDINE TABLETS, 300 MG - GENEVA (V)
RANITIDINE-ENTERIC-COATED TABLET (V)
RANTIDINE (V)
SOSTRIL (V)
SOSTRIL (RANITIDINE) (V)
TRITEC (V)
UNKNOWN RANITIDINE (V)
ZANTAC (FORMULATION UNKNOWN) (RANITIDINE HYDROCHLORIDE) (V)
ZANTAC 75 (V)
ZANTAC SYRUP (RANITIDINE) (V)
ZANTIC (V)
ZANTIC (RANITIDINE HYDROCHLORIDE) (V)
ZANTIC (RANITIDINE HYDROCHLORIDE) GLAXO LABORATORIES LIMITED (V)
ZANTIC (RANITIDINE) (V)

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1982	2	1	1	0	1	0	0	0	0
	4	2	2	2	0	0	0	0	0
	Subtotal	3	3	2	1	0	0	0	0
1983	3	5	2	0	2	0	0	0	0
	4	73	23	4	21	0	0	0	0
	Subtotal	78	25	4	23	0	0	0	0
1984	1	96	22	4	21	0	0	0	0
	2	121	29	2	27	0	0	0	0
	3	164	26	3	25	0	0	0	0
	4	73	18	4	15	0	0	0	0
	Subtotal	454	95	13	88	0	0	0	0
1985	1	104	17	4	14	0	0	0	0
	2	37	18	6	17	0	0	0	0
	3	133	19	0	19	0	0	0	0
	4	33	18	3	18	0	0	0	0
	Subtotal	307	72	13	68	0	0	0	0
1986	1	116	19	5	17	0	0	0	0
	2	96	25	4	24	0	0	0	0
	3	113	31	6	27	0	1	0	0
	4	48	18	5	15	0	0	0	0
	Subtotal	373	93	20	83	0	1	0	0
1987	1	78	27	1	22	0	4	0	0
	2	128	42	16	27	0	1	0	0
	3	277	24	2	20	0	3	0	0
	4	43	21	6	19	0	0	0	0
	Subtotal	526	114	25	88	0	8	0	0
1988	1	25	13	0	13	0	0	0	0
	2	40	17	3	14	0	0	0	0
	3	292	23	7	22	0	0	0	0
	4	112	22	3	20	0	1	0	0
	Subtotal	469	75	13	69	0	1	0	0

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Search Criteria Name: CORKENA Search submitted on: 05-31-2000 10:19:49
Product/Group Name: RANITIDINE (A)
Reaction/Group Name:
Search Case Count9013

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FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1989	1	35	22	5	14	0	4	0	0
	2	54	31	3	29	0	1	0	0
	3	446	36	5	31	0	1	0	0
	4	130	29	4	26	0	1	0	0
	Subtotal	665	118	17	100	0	7	0	0
1990	1	43	22	7	15	0	2	0	0
	2	38	14	2	11	0	2	0	0
	3	370	20	5	15	0	3	0	0
	4	109	19	2	16	0	1	0	0
	Subtotal	560	75	16	57	0	8	0	0
1991	1	43	16	6	12	0	1	0	0
	2	45	18	5	13	0	3	0	0
	3	399	30	8	23	0	6	0	0
	4	101	19	2	18	0	0	0	0
	Subtotal	588	83	21	66	0	10	0	0
1992	1	29	10	2	8	0	2	0	0
	2	46	24	5	17	0	3	0	0
	3	569	26	3	19	1	6	0	0
	4	98	25	2	22	0	1	0	0
	Subtotal	742	85	12	66	1	12	0	0
1993	1	33	9	1	8	0	1	0	0
	2	39	23	5	17	0	3	0	0
	3	719	40	5	26	3	3	0	2
	4	77	22	4	14	4	1	0	4
	Subtotal	868	94	15	65	7	8	0	6
1994	1	74	37	5	19	4	5	0	1
	2	45	33	1	17	4	4	0	4
	3	334	34	2	16	5	2	0	7
	4	76	30	1	22	2	1	0	5
	Subtotal	529	134	9	74	15	12	0	17

APPEARS THIS WAY
ON ORIGINAL

Search Criteria Name: CORKENA Search submitted on: 05-31-2000 10:19:49
Product/Group Name: RANITIDINE (A)
Reaction/Group Name:
Search Case Count2013

FDA - Adverse Event Reporting System (AERS)
Standard Report
Cases by Year and Quarter

Year	Quarter	Total Count	Serious	Death	Hospitalized	Life Threatening	Disabled	Congenital Anomaly	Required Intervention
1995	1	82	31	3	18	1	3	1	4
	2	64	37	4	25	0	0	0	0
	3	482	29	7	17	3	1	1	2
	4	96	22	1	7	3	3	0	3
	Subtotal	724	119	15	67	7	7	2	9
1996	1	85	23	1	9	4	1	0	5
	2	65	30	5	12	9	4	0	4
	3	762	28	4	10	7	3	0	4
	4	270	12	0	6	1	1	0	6
	Subtotal	1182	93	10	37	21	9	0	19
1997	1	190	30	1	7	3	2	0	2
	2	159	11	1	4	1	1	0	1
	3	3	1	0	0	0	0	0	0
	4	24	16	1	2	3	1	0	0
	Subtotal	376	58	3	13	7	4	0	3
1998	1	34	29	0	4	0	2	0	1
	2	27	24	1	9	1	1	0	2
	3	29	24	0	10	1	0	0	0
	4	25	19	0	6	2	1	0	4
	Subtotal	115	96	1	29	4	4	0	7
1999	1	179	27	2	9	1	1	0	9
	2	17	14	0	4	0	1	0	1
	3	193	29	1	13	2	0	0	3
	4	24	17	2	6	2	0	0	1
	Subtotal	413	87	5	32	5	2	0	14
2000	1	41	34	2	11	1	2	0	7
	Subtotal	41	34	2	11	1	2	0	7
Total		9013	1553	216	1037	68	95	2	82

APPEARS THIS WAY
ON ORIGINAL

Search Criteria Name: CORKENA Search submitted on: 05-31-2000 10:19:49
Product/Group Name: RANITIDINE (A)
Reaction/Group Name:
Search Case Count9013

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Adverse Event Reporting System (AERS)

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 05/31/2000 - 11:04 am

Search Criteria:

Product Name(s):

- RANITIDINE (A)
- RANITIDINE BISMUTH CITRATE (A)
- RANITIDINE HYDROCHLORIDE (A)
- ZANTAC (RANITIDINE) (V)
- ZANTAC (T)
- ZANTAC (V)
- ZANTAC 75 OTC TABLET (V)
- ZANTAC 300MG (V)
- ZANTAC 50 MG (V)
- ZANTAC 75 OTC TABLET (V)
- ZANTAC-75 WARNER-LAMBERT (RANITIDINE) (V)

Manufacturer Type Sender of ISR

Search Type: CASE

Search for reactions listed: ANY

FDA Recvd. Date: From:

Reporter Domestic: YES

Reporter First Name:

Null Values for Country

Female:

Age Range: From

MedWatch Source Study

MedWatch Source Health Professional:

Expedited (15-Day) ISR:

RA Summary ISR

Include Deactived ISRs

Non-Serious Outcome:

Event End Date:

OTC Products Only:

Include Concomitant Products:

ISR/Case #:

FDA Recvd. Date: To: 03/31/2000

Reporter Foreign:

Reporter City:

Patient ID:

Gender Unknown:

Age Range: To:

MedWatch Source Literature

Direct ISR:

10 Day ISR:

Initial:

Processed ISRs/Cases Only: YES

ISRs with No Outcome Reported:

DeC:

Include Combination Products

Mfr. Control #:

Sort in Descending Order

Reporter Last Name

Reporter State

Male

Null Gender Value

Age Range: YEAR

MedWatch Source Consumer

Periodic ISR

5 Day ISR

Follow-up

Serious Outcome

Event Start Date:

ReC

Adverse Event Reporting System (AEI

Standard Report

All Preferred Terms in Cases

Run by: ANN CORKEN Date - Time: 05/31/2000 - 11:04 am

Non-Excluded Product(s) for Selected Active Ingredient(s):

RANITIDINE (T)
ZANTAC (T)
AZANTAC (V)
AZANTAC (RANITIDINE) UNKNOWN (V)
AZANTAC\150 (V)
GENERIC RANITIDINE (150 MG OR 300 MG) (V)
RANIPLEX (V)
RANITIDIN (RANITIDINE) (V)
RANITIDINE (V)
RANITIDINE 300MG (V)
RANITIDINE HYDROCHLORIDE (RANITIDINE) TABLET (V)
RANITIDINE TABLETS, 300 MG - GENEVA (V)
SOSTRIL (RANITIDINE) (V)
ZANTAC 75 (V)
ZANTIC (RANITIDINE HYDROCHLORIDE) GLAXO LABORATORIES LIMITED (V)
RANITIDINE HCL (T)
ZANTAC 150 (T)
AZANTAC 150 MG (V)
AZANTAC / 150 (V)
CALCIUM CARBONATE (V)
GENEVA GENERICS (V)
RANIPLEX (RANITIDINE HCL) (V)
RANITIDIN SOLUTION FOR INJECTION (V)
RANITIDINE /50 MG GENEVA (V)
RANITIDINE HYDROCHLORIDE (V)
RANITIDINE TABLET (RANITIDINE HYDROCHLORIDE) (V)
RANITIDINE-ENTERIC-COATED TABLET (V)
TRITEC (V)
ZANTAC SYRUP (RANITIDINE) (V)
ZANTIC (RANITIDINE) (V)
RANITIDINE HYDROCHLORIDE (T)
ZANTAC 300 (T)
AZANTAC (RANITIDINE HCL) (V)
AZANTAC 150 MG (V)
CEFTAZIDINE (MODACINE) (V)
RANI 2(RANITIDINE HCL) (V)
RANIPLEX (RANITIDINE) (V)
RANITIDIN TABLETS (V)
RANITIDINE 150MG (V)
RANITIDINE HYDROCHLORIDE (AZANTAC) SOLUTION FOR INJECTION (V)
RANITIDINE TABLETS USP (V)
RANTIDINE (V)
UNKNOWN RANITIDINE (V)
ZANTIC (V)
TRITEC (T)
ZANTAC 75 (T)
AZANTAC (RANITIDINE) (V)
AZANTAC INJECTABLE SOLUTION (V)
GENERIC RANITADINE (V)
RANIDIL (V)
RANITIC (RANITIDINE) 150 MG (V)
RANITIDINA (RANITIDINE) (V)
RANITIDINE 300 MG BID (V)
RANITIDINE HYDROCHLORIDE (FORMULATION UNKNOWN) (V)
RANITIDINE TABLETS, 150 MG APOTEX LABEL (V)
SOSTRIL (V)
ZANTAC (FORMULATION UNKNOWN) (RANITIDINE HYDROCHLORIDE) (V)
ZANTIC (RANITIDINE HYDROCHLORIDE) (V)

Excluded Product(s) for Selected Active Ingredient(s):

FDA - Adverse Event Rep[illegible]g System (AERS)
Standard[illegible]rt
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Drug Ineffective	868	9.63	U
Thrombocytopenia	478	5.30	U
Abdominal Pain Nos	461	5.11	U
Dermatitis Nos	458	5.08	U
Headache Nos	442	4.90	U
Pruritus	412	4.57	U
Confusion	400	4.44	U
Diarrhoea Nos	357	3.96	U
Nausea	328	3.64	U
Dyspepsia	302	3.35	U
Dizziness (Exc Vertigo)	293	3.25	U
Hepatic Function Abnormal Nos	290	3.22	U
Drug Interaction Nos	288	3.20	U
Hypersensitivity Nos	259	2.87	U
Urticaria Nos	250	2.77	U
Alopecia	240	2.66	U
Vomiting Nos	238	2.64	U
Pyrexia	207	2.30	U
Condition Aggravated	192	2.13	U
Asthenia	177	1.96	U
Leucopenia Nos	171	1.90	U
Hallucination Nos	161	1.79	U
Insomnia Nec	160	1.78	U
Sedation	150	1.66	U
Dyspnoea Nos	142	1.58	U
Hepatitis Nos	138	1.53	U
Chest Pain	133	1.48	U
Flatulence	128	1.42	U
Face Oedema	119	1.32	U
Constipation	117	1.30	U
Paraesthesia Nec	115	1.28	U
Depression Nec	114	1.26	U
Pain Nos	109	1.21	U
Arthralgia	105	1.16	U
Blood Alkaline Phosphatase Nos Increased	105	1.16	U
Tachycardia Nos	104	1.15	U
Drug Level Nos Above Therapeutic	101	1.12	U
Aspartate Aminotransferase Increased	100	1.11	U

Search Criteria Name:CORKENA Search submitted on: 05-31-2000 10:19:49
Product/Group Name:RANITIDINE (A)
Reaction/Group Name:
Search Case Count:9013

FDA - Adverse Event Reporting System (AERS)
Standard Report
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Impotence	99	1.10	U
Malaise	98	1.09	U
Agitation	97	1.08	U
Alanine Aminotransferase Increased	97	1.08	U
Gynaecomastia	92	1.02	U
Nervousness	92	1.02	U
Blood Bilirubin Increased	90	1.00	U
Tremor Nec	88	0.98	U
Myalgia	87	0.97	U
Anaphylactic Reaction	85	0.94	U
Amblyopia Nos	82	0.91	U
Pharyngitis Nos	82	0.91	U
Rash Maculo-Papular	80	0.89	U
Taste Disturbance	80	0.89	U
Dry Mouth	77	0.85	U
Vasodilatation	76	0.84	U
Jaundice Nos	75	0.83	U
Injection Site Reaction Nos	74	0.82	U
Amnesia Nec	73	0.81	U
Anxiety Nec	72	0.80	U
Asthma Nos	69	0.77	U
Hypotension	64	0.71	U
Blood Creatinine Increased	63	0.70	U
Oedema Nos	60	0.67	U
Breast Pain	58	0.64	U
Convulsions Nos	58	0.64	U
Pancreatitis Nos	58	0.64	U
Sweating Increased	57	0.63	U
Oedema Peripheral	56	0.62	U
Hypertension Nos	55	0.61	U
Prothrombin Level Decreased	55	0.61	U
Gastrointestinal Disorder Nos	54	0.60	U
Faecal Abnormality Nos	53	0.59	U
Palpitations	53	0.59	U
Pancytopenia	53	0.59	U
Bradycardia Nos	52	0.58	U
Rhinitis Nos	50	0.55	U
Unexpected Therapeutic Effect	50	0.55	U

PT	Count of PTs	Percent of Total	Labeled
Libido Decreased	48	0.53	U
Urine Abnormal Nos	48	0.53	U
Thinking Abnormal Nec	47	0.52	U
Abnormal Dreams	44	0.49	U
Jaundice Cholestatic	44	0.49	U
Tinnitus	44	0.49	U
Anaemia Nos	43	0.48	U
Eosinophilia (Exc Pulmonary)	43	0.48	U
Dysphagia	42	0.47	U
Syncope	42	0.47	U
Unevaluable Reaction	42	0.47	U
Arrhythmia Nos	40	0.44	U
Psychotic Disorder Nos	39	0.43	U
Stomatitis	39	0.43	U
Back Pain	38	0.42	U
Blood Urea Increased	38	0.42	U
Oesophagitis	38	0.42	U
Hostility	37	0.41	U
Overdose Nos	37	0.41	U
Cough	36	0.40	U
Dermatitis Bullous	36	0.40	U
Iron Deficiency Anaemia	36	0.40	U
Vertigo Nec	36	0.40	U
Breast Enlargement	35	0.39	U
Eructation	35	0.39	U
Urinary Frequency	34	0.38	U
Anorexia	33	0.37	U
Leucocytosis Nos	33	0.37	U
Drug Maladministration	32	0.36	U
Gastrointestinal Haemorrhage Nos	32	0.36	U
Phlebitis Nos	32	0.36	U
Urinary Retention	32	0.36	U
Delirium	31	0.34	U
Galactorrhoea	31	0.34	U
Laryngospasm	31	0.34	U
Weight Increased	31	0.34	U
Angioneurotic Oedema	30	0.33	U
Cardiac Arrest	30	0.33	U

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PT	Count of PTs	Percent of Total	Labeled
Weight Decreased	30	0.33	U
Accidental Overdose (Therapeutic Agent)	29	0.32	U
Apnoea	29	0.32	U
Blood Lactate Dehydrogenase Increased	29	0.32	U
Erythema Multiforme	29	0.32	U
Influenza Like Illness	29	0.32	U
Speech Disorder Nec	29	0.32	U
Agranulocytosis	28	0.31	U
Arthritis Nos	28	0.31	U
Glossitis	28	0.31	U
Peripheral Neuropathy Nec	28	0.31	U
Pneumonia Nos	28	0.31	U
Rigors	28	0.31	U
Bone Marrow Depression Nos	27	0.30	U
Hepatocellular Damage	27	0.30	U
Hypertonia	27	0.30	U
Laboratory Test Abnormal Nos	27	0.30	U
Vasculitis Nos	27	0.30	U
Stupor	26	0.29	U
Dysuria	25	0.28	U
Haematuria Present	25	0.28	U
Injection Site Pain	25	0.28	U
Muscle Twitching	25	0.28	U
Photosensitivity Reaction Nos	25	0.28	U
Ventricular Extrasystoles	25	0.28	U
Vision Abnormal Nec	25	0.28	U
Blood Amylase Increased	24	0.27	U
Conjunctivitis Nec	24	0.27	U
Drug Level Nos Below Therapeutic	24	0.27	U
Ecchymosis	24	0.27	U
Gastrointestinal Tract Cancer Nos	24	0.27	U
Hypercholesterolaemia	24	0.27	U
Hypoglycaemia Nos	24	0.27	U
Infection Nos	24	0.27	U
Paranoia	24	0.27	U
Gastritis Nos	23	0.26	U
Abdominal Distension	22	0.24	U
Dermatitis Exfoliative Nos	22	0.24	U

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Standard [illegible]rt
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Gamma-Glutamyltransferase Increased	22	0.24	U
Personality Disorder Nos	22	0.24	U
Sepsis Nos	22	0.24	U
Aplastic Anaemia	21	0.23	U
Colitis Nos	21	0.23	U
Death	21	0.23	U
Dry Skin	21	0.23	U
Hyperglycaemia Nos	21	0.23	U
Migraine Nos	21	0.23	U
Nephritis Nos	21	0.23	U
Renal Failure Nos	21	0.23	U
Coma Nec	20	0.22	U
Drug Withdrawal Syndrome	20	0.22	U
Haemolytic Anaemia Nos	20	0.22	U
Injection Site Necrosis	20	0.22	U
Non-Accidental Overdose	20	0.22	U
Atrial Fibrillation	19	0.21	U
Emotional Disturbance Nos	19	0.21	U
Myasthenic Syndrome	19	0.21	U
Renal Failure Acute	19	0.21	U
Skin Discolouration	19	0.21	U
Tongue Oedema	19	0.21	U
Ataxia Nec	18	0.20	U
Cholelithiasis	18	0.20	U
Extrapyramidal Disorder Nec	18	0.20	U
Idiopathic Thrombocytopenic Purpura	18	0.20	U
Myocardial Infarction	18	0.20	U
Abdominal Pain Upper	17	0.19	U
Renal Impairment Nos	17	0.19	U
Deafness Nos	16	0.18	U
Drug Effect Increased	16	0.18	U
Grand Mal Convulsion	16	0.18	U
Haemorrhage Nos	16	0.18	U
Tolerance Increased	16	0.18	U
Alcohol Intolerance	15	0.17	U
Carcinoma Nos	15	0.17	U
Coordination Abnormal Nos	15	0.17	U
Depersonalisation	15	0.17	U

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PT	Count of PTs	Percent of Total	Labeled
Hyperventilation	15	0.17	U
Salivary Hypersecretion	15	0.17	U
Accident Nos	14	0.16	U
Breast Neoplasm Nos	14	0.16	U
Cerebrovascular Accident Nos	14	0.16	U
Epistaxis	14	0.16	U
Eye Pain	14	0.16	U
Hypoaesthesia	14	0.16	U
Hyponatraemia	14	0.16	U
Melaena	14	0.16	U
Taste Loss	14	0.16	U
Vaginitis	14	0.16	U
Acne Nos	13	0.14	U
Cyst Nos	13	0.14	U
Dehydration	13	0.14	U
Dementia Nos	13	0.14	U
Diplopia	13	0.14	U
Hypokalaemia	13	0.14	U
Paresthesia Circumoral	13	0.14	U
Parosmia	13	0.14	U
Suicide Attempt	13	0.14	U
Thrombocythaemia	13	0.14	U
Delusion Nos	12	0.13	U
Encephalopathy Nos	12	0.13	U
Hirsutism	12	0.13	U
Hyperkinetic Syndrome	12	0.13	U
Lymphadenopathy	12	0.13	U
Mouth Ulceration	12	0.13	U
Movement Disorder Nos	12	0.13	U
Muscle Cramps	12	0.13	U
Nail Disorder Nos	12	0.13	U
Oliguria	12	0.13	U
Purpura Nos	12	0.13	U
Skin Disorder Nos	12	0.13	U
Urinary Incontinence	12	0.13	U
Antinuclear Factor Positive	11	0.12	U
Cystitis Nos	11	0.12	U
Hair Disorder Nos	11	0.12	U

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FDA - Adverse Event Reporting System (AERS)
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PT	Count of PTs	Percent of Total	Labeled
Laboratory Test Interference Nos	11	0.12	U
Lacrimal Disorder Nos	11	0.12	U
Major Depressive Disorder Nos	11	0.12	U
Petechiae	11	0.12	U
Ventricular Tachycardia	11	0.12	U
Albuminuria Present	10	0.11	U
Atrioventricular Block Nos	10	0.11	U
Cholecystitis Nos	10	0.11	U
Drug Dependence	10	0.11	U
Erythrocyte Sedimentation Rate Increased	10	0.11	U
Gait Abnormal Nos	10	0.11	U
Haematemesis	10	0.11	U
Peptic Ulcer	10	0.11	U
Respiratory Disorder Nos	10	0.11	U
Right Ventricular Failure	10	0.11	U
Sexual Dysfunction Nos	10	0.11	U
Supraventricular Tachycardia	10	0.11	U
Urinary Tract Infection Nos	10	0.11	U
Acute Circulatory Failure	9	0.10	U
Aphasia	9	0.10	U
Arthrosis Nos	9	0.10	U
Bone Pain	9	0.10	U
Central Nervous System Depression Nos	9	0.10	U
Dyskinesia Nec	9	0.10	U
Dystonia	9	0.10	U
Eye Disorder Nos	9	0.10	U
Fatigue	9	0.10	U
Hair Colour Changes	9	0.10	U
Hepatic Neoplasm Malignant Nos	9	0.10	U
Inappropriate Adh Secretion	9	0.10	U
Infertility Male	9	0.10	U
Peripheral Vascular Disease Nos	9	0.10	U
Platelet Count Decreased	9	0.10	U
Postural Hypotension	9	0.10	U
Prostatic Disorder Nos	9	0.10	U
Rectal Bleeding	9	0.10	U
Vaginal Haemorrhage	9	0.10	U
Weakness	9	0.10	U

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Search Criteria Name:CORKENA Search submitted on: 05-31-2000 10:19:49
Product/Group Name:RANITIDINE (A)
Reaction/Group Name:
Search Case Count:9013

PT	Count of PTs	Percent of Total	Labeled
Blood Creatine Phosphokinase Increased	8	0.09	U
Coombs Positive Haemolytic Anaemia	8	0.09	U
Diabetes Mellitus Nos	8	0.09	U
Drug Effect Decreased	8	0.09	U
Dysphonia	8	0.09	U
Faeces Discoloured	8	0.09	U
Gastric Ulcer	8	0.09	U
Gingivitis	8	0.09	U
Hepatomegaly	8	0.09	U
Hyperkalaemia	8	0.09	U
Injection Site Hypersensitivity	8	0.09	U
Intestinal Obstruction Nos	8	0.09	U
Liver Fatty	8	0.09	U
Myopathy	8	0.09	U
Pulmonary Oedema Nos	8	0.09	U
Tongue Discolouration Nos	8	0.09	U
Application Site Reaction Nos	7	0.08	U
Bronchitis Nos	7	0.08	U
Burning Sensation Nos	7	0.08	U
Coagulation Disorder Nos	7	0.08	U
Congenital Abnormality Nos	7	0.08	U
Cyanosis Nos	7	0.08	U
Extrasystoles Nos	7	0.08	U
Eye Haemorrhage Nec	7	0.08	U
Fibrocystic Breast Disease	7	0.08	U
Gingival Bleeding	7	0.08	U
Haemoptysis	7	0.08	U
Hyperlipidaemia Nos	7	0.08	U
Hypoproteinaemia	7	0.08	U
Joint Disorder Nos	7	0.08	U
Lipase Increased	7	0.08	U
Menometrorrhagia	7	0.08	U
Neoplasm Nos	7	0.08	U
Nystagmus Nos	7	0.08	U
Oesophageal Reflux	7	0.08	U
Polyuria	7	0.08	U
Stevens Johnson Syndrome	7	0.08	U
Tooth Disorder Nos	7	0.08	U

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PT	Count of PTs	Percent of Total	Labeled
Vision Blurred	7	0.08	U
Accommodation Disorder	6	0.07	U
Amenorrhoea Nos	6	0.07	U
Angina Pectoris	6	0.07	U
Cardiospasm	6	0.07	U
Cerebr l Ischaemia	6	0.07	U
Coomt Direct Test Positive	6	0.07	U
Di Ticul y In Micturition	6	0.07	U
Dry Eye Nec	6	0.07	U
Duodenal Ulcer Perforation	6	0.07	U
Dyspepsia Aggravated	6	0.07	U
Earache	6	0.07	U
Enzyme Abnormality Nos	6	0.07	U
Epidermal Necrolysis	6	0.07	U
Hyperaesthesia	6	0.07	U
Hypotonia	6	0.07	U
Ileus	6	0.07	U
Irritability	6	0.07	U
Liver Function Tests Nos Abnormal	6	0.07	U
Loss Of Consciousness Nec	6	0.07	U
Lung Disorder Nos	6	0.07	U
Myositis	6	0.07	U
Nephrotic Syndrome	6	0.07	U
Oral Candidiasis	6	0.07	U
Prothrombin Level Increased	6	0.07	U
Psoriasis	6	0.07	U
Rash Pustular	6	0.07	U
Sinusitis Nos	6	0.07	U
Sleep Disorder Nos	6	0.07	U
Stridor	6	0.07	U
Tenosynovitis	6	0.07	U
Thrombosis Nos	6	0.07	U
Blood Dyscrasia Nos	5	0.06	U
Blood Pressure Increased	5	0.06	U
Cardiac Failure Nos	5	0.06	U
Choreoathetosis	5	0.06	U
Colitis Pseudomembranous	5	0.06	U
Deafness Transitory	5	0.06	U

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PT	Count of PTs	Percent of Total	Labeled
Duodenitis	5	0.06	U
Ejaculation Disorder Nos	5	0.06	U
Enteritis	5	0.06	U
Granuloma Nos	5	0.06	U
Halitosis	5	0.06	U
Hepatic Cirrhosis Nos	5	0.06	U
Hepatic Failure	5	0.06	U
Hepatic Necrosis	5	0.06	U
Hepatorenal Syndrome	5	0.06	U
Herpes Zoster	5	0.06	U
Hiccups	5	0.06	U
Hyperuricaemia	5	0.06	U
Laryngitis Nos	5	0.06	U
Loose Stools	5	0.06	U
Menstrual Disorder Nos	5	0.06	U
Micturition Urgency	5	0.06	U
Myoclonic Jerks	5	0.06	U
Neck Stiffness	5	0.06	U
Nephritis Interstitial	5	0.06	U
Neuralgia Nos	5	0.06	U
Pallor	5	0.06	U
Photophobia	5	0.06	U
Porphyria Nos	5	0.06	U
Pulmonary Fibrosis	5	0.06	U
Rash Erythematous	5	0.06	U
Rectal Disorder Nos	5	0.06	U
Serum Sickness	5	0.06	U
Systemic Lupus Erythematosus	5	0.06	U
Tablet In Stool	5	0.06	U
Visual Field Defect Nos	5	0.06	U
Abscess Nos	4	0.04	U
Aggression	4	0.04	U
Akathisia	4	0.04	U
Anaemia Vitamin B12 Deficiency	4	0.04	U
Atrioventricular Block Second Degree	4	0.04	U
Bleeding Time Prolonged	4	0.04	U
Blister	4	0.04	U
Blood Thromboplastin Decreased	4	0.04	U

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PT	Count of PTs	Percent of Total	Labeled
Bone Disorder Nos	4	0.04	U
Breast Engorgement	4	0.04	U
Cardiovascular Disorder Nos	4	0.04	U
Cheilitis	4	0.04	U
Coagulation Time Nos Prolonged	4	0.04	U
Dermatitis Contact	4	0.04	U
Electrocardiogram Qt Prolonged	4	0.04	U
Euphoric Mood	4	0.04	U
Fall	4	0.04	U
Haemolysis Nos	4	0.04	U
Haemorrhagic Stroke	4	0.04	U
Hypercalcaemia	4	0.04	U
Hypergammaglobulinaemia	4	0.04	U
Hyperthyroidism	4	0.04	U
Hyporeflexia	4	0.04	U
Hypovitaminosis Nos	4	0.04	U
Injection Site Oedema	4	0.04	U
Laryngeal Oedema	4	0.04	U
Leukaemia Nos	4	0.04	U
Lung Cancer Stage Unspecified (Exc Metastatic Tumours To Lung)	4	0.04	U
Megacolon Nos	4	0.04	U
Mucous Membrane Disorder Nos	4	0.04	U
Muscle Rigidity	4	0.04	U
Neutropenia	4	0.04	U
Nocturia	4	0.04	U
Oculogyric Crisis	4	0.04	U
Pathological Fracture	4	0.04	U
Platelet Abnormalities Nos	4	0.04	U
Rash Generalised	4	0.04	U
Respiratory Arrest (Exc Neonatal)	4	0.04	U
Sinus Bradycardia	4	0.04	U
Sputum Increased	4	0.04	U
Thirst	4	0.04	U
Tongue Disorder Nos	4	0.04	U
Urinary Tract Disorder Nos	4	0.04	U
Ventricular Fibrillation	4	0.04	U
Vestibular Disorder Nos	4	0.04	U

PT	Count of PTs	Percent of Total	Labeled
Appetite Decreased	3	0.03	U
Appetite Increased	3	0.03	U
Ascites	3	0.03	U
Atrioventricular Block Complete	3	0.03	U
Bacterial Infection Nos	3	0.03	U
Bezoar	3	0.03	U
Blood Thromboplastin Increased	3	0.03	U
Calculus Renal Nos	3	0.03	U
Cardiac Disorder Nos	3	0.03	U
Catatonia	3	0.03	U
Cholangitis Nos	3	0.03	U
Coagulation Time Nos Shortened	3	0.03	U
Collapse	3	0.03	U
Creatinine Renal Clearance Decreased	3	0.03	U
Depressed Level Of Consciousness	3	0.03	U
Diabetes Insipidus	3	0.03	U
Disorder Neonatal Nos	3	0.03	U
Drug Hypersensitivity	3	0.03	U
Duodenal Ulcer Haemorrhage	3	0.03	U
Electrocardiogram Abnormal Nos	3	0.03	U
Electroencephalogram Abnormal	3	0.03	U
Feeling Abnormal	3	0.03	U
Flushing	3	0.03	U
Gastric Ulcer Haemorrhage	3	0.03	U
Gastrointestinal Neoplasm Nos	3	0.03	U
Glaucoma Nos	3	0.03	U
Glossodynia	3	0.03	U
Gout	3	0.03	U
Graft Rejection	3	0.03	U
Hemiplegia	3	0.03	U
Hepatitis C	3	0.03	U
Hiatus Hernia	3	0.03	U
Hormone Level Nos Abnormal	3	0.03	U
Hypernatraemia	3	0.03	U
Hypothermia	3	0.03	U
Hypoxia	3	0.03	U
Infertility Female	3	0.03	U
Keratoconjunctivitis	3	0.03	U

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PT	Count of PTs	Percent of Total	Labeled
Ketoacidosis	3	0.03	U
Lethargy	3	0.03	U
Liver Tenderness	3	0.03	U
Mania	3	0.03	U
Megaloblastic Anaemia Nos	3	0.03	U
Mesenteric Occlusion	3	0.03	U
Muscle Spasms	3	0.03	U
Mydriasis	3	0.03	U
Myeloid Maturation Arrest	3	0.03	U
Myocarditis Nos	3	0.03	U
Neck Pain	3	0.03	U
Neurosis Nos	3	0.03	U
Oedema Upper Limb	3	0.03	U
Oesophageal Reflux Aggravated	3	0.03	U
Oesophageal Ulcer	3	0.03	U
Opisthotonus	3	0.03	U
Optic Neuritis Nec	3	0.03	U
Oxygen Saturation Decreased	3	0.03	U
Pain In Limb	3	0.03	U
Pancreatitis Haemorrhagic	3	0.03	U
Parotid Gland Enlargement	3	0.03	U
Peptic Ulcer Haemorrhage	3	0.03	U
Pericardial Effusion	3	0.03	U
Prostate Cancer Nos	3	0.03	U
Prostatic Specific Antigen Increased	3	0.03	U
Pupillary Disorder Nos	3	0.03	U
Red Blood Cell Abnormality Nos	3	0.03	U
Renal Tubular Necrosis	3	0.03	U
Respiratory Acidosis	3	0.03	U
Screaming	3	0.03	U
Seborrhoea	3	0.03	U
Skin Necrosis	3	0.03	U
Skin Neoplasm Nos	3	0.03	U
Skin Nodule	3	0.03	U
Skin Odour Abnormal	3	0.03	U
Suturing	3	0.03	U
Tatus Epilepticus	3	0.03	U
Subdural Haematoma	3	0.03	U

PT	Count of PTs	Percent of Total	Labeled
Supraventricular Extrasystoles	3	0.03	U
Testicular Disorder Nos	3	0.03	U
Therapeutic Response Decreased	3	0.03	U
Throat Irritation	3	0.03	U
Thromboembolism Nos	3	0.03	U
Thyroid Disorder Nos	3	0.03	U
Tooth Caries Nos	3	0.03	U
Torticollis	3	0.03	U
Viral Infection Nos	3	0.03	U
Visual Disturbance Nos	3	0.03	U
Vitreous Disorder Nos	3	0.03	U
White Blood Cell Disorder Nos	3	0.03	U
Abnormal Behaviour Nos	2	0.02	U
Achlorhydria	2	0.02	U
Acidosis Nos	2	0.02	U
Acute Abdomen	2	0.02	U
Alkalosis Nos	2	0.02	U
Amyloidosis Nos	2	0.02	U
Anuria	2	0.02	U
Atrioventricular Block First Degree	2	0.02	U
Benign Intracranial Hypertension	2	0.02	U
Blepharitis	2	0.02	U
Blood Electrolytes Nos Abnormal	2	0.02	U
Blood Prolactin Increased	2	0.02	U
Bronchospasm Nos	2	0.02	U
Buccoglossal Syndrome	2	0.02	U
Cardio-Respiratory Arrest	2	0.02	U
Cataract Nec	2	0.02	U
Cellulitis	2	0.02	U
Central Nervous System Stimulation Nos	2	0.02	U
Cerebellar Ataxia	2	0.02	U
Cerebrovascular Disorder Nos	2	0.02	U
Choking Sensation	2	0.02	U
Colour Blindness Nec	2	0.02	U
Completed Suicide	2	0.02	U
Convulsions Nos Aggravated	2	0.02	U
Corneal Lesion Nos	2	0.02	U
Crying	2	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Culture Urine Positive	2	0.02	U
Dermatitis Lichenoid	2	0.02	U
Diarrhoea Haemorrhagic	2	0.02	U
Digoxin Toxicity	2	0.02	U
Discomfort Nos	2	0.02	U
Disorientation	2	0.02	U
Drug Toxicity Nos	2	0.02	U
Dysarthria	2	0.02	U
Ear Disorder Nos	2	0.02	U
Endometrial Hyperplasia	2	0.02	U
Epilepsy Aggravated	2	0.02	U
Erythema Nec	2	0.02	U
Erythema Nodosum	2	0.02	U
Eye Irritation	2	0.02	U
Eye Rolling	2	0.02	U
Facial Palsy	2	0.02	U
Feeling Cold	2	0.02	U
Fibromyalgia Syndrome	2	0.02	U
Fungal Infection Nos	2	0.02	U
Gastric Atony	2	0.02	U
Gastritis Haemorrhagic	2	0.02	U
Gastrointestinal Candidiasis	2	0.02	U
Glomerulonephritis Nos	2	0.02	U
Haemoglobin Decreased	2	0.02	U
Heart Rate Increased	2	0.02	U
Hepatosplenomegaly	2	0.02	U
Hepatotoxicity Nos	2	0.02	U
Hyperpituitarism Nos	2	0.02	U
Hypocalcaemia	2	0.02	U
Hypothyroidism	2	0.02	U
Hypoventilation	2	0.02	U
Immune System Disorder Nos	2	0.02	U
Injection Site Haemorrhage	2	0.02	U
Joint Stiffness	2	0.02	U
Kidney Transplant Rejection	2	0.02	U
Lactic Acidosis	2	0.02	U
Lactose Intolerance	2	0.02	U
Lung Function Decreased	2	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Toxicology Nos Abnormal	1	0.01	U
Ulcer Nos	1	0.01	U
Ultrasound Scan Nos Abnormal	1	0.01	U
Umbilical Hernia Nos	1	0.01	U
Upper Respiratory Tract Infection Nos	1	0.01	U
Uraemic Encephalopathy	1	0.01	U
Urethral Pain	1	0.01	U
Urinary Casts	1	0.01	U
Urinary Tract Infection Enterococcal	1	0.01	U
Urine Analysis Abnormal Nos	1	0.01	U
Urine Discolouration	1	0.01	U
Uterine Fibroids	1	0.01	U
Uveitis Nos	1	0.01	U
Vaginal Candidiasis	1	0.01	U
Varicose Veins Nos	1	0.01	U
Vascular Anomaly Nos	1	0.01	U
Venous Thrombosis Deep Limb	1	0.01	U
Ventricular Hypertrophy	1	0.01	U
Weight Gain Poor	1	0.01	U
White Blood Cell Count Increased	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Malabsorption	2	0.02	U
Memory Impairment	2	0.02	U
Methaemoglobinaemia Nos	2	0.02	U
Miosis	2	0.02	U
Mottled Skin	2	0.02	U
Myeloproliferative Disorder Nos	2	0.02	U
Nasal Congestion	2	0.02	U
Necrosis	2	0.02	U
Nephropathy Toxic	2	0.02	U
Nephrosclerosis	2	0.02	U
Neutrophilia	2	0.02	U
Oedema Lower Limb	2	0.02	U
Oesophageal Disorder Nos	2	0.02	U
Oligomenorrhoea Nos	2	0.02	U
Ovarian Disorder Nos	2	0.02	U
Paraplegia	2	0.02	U
Peptic Ulcer Perforation	2	0.02	U
Pleural Disorder Nos	2	0.02	U
Pleural Effusion	2	0.02	U
Pneumonitis Aspiration	2	0.02	U
Pulmonary Haemorrhage	2	0.02	U
Pulsus Bigeminus	2	0.02	U
Pupils Unequal	2	0.02	U
Pyuria	2	0.02	U
Rash Papular	2	0.02	U
Refractive Errors Nos	2	0.02	U
Retching	2	0.02	U
Reticuloendothelial System Stimulated	2	0.02	U
Rheumatoid Arthritis	2	0.02	U
Sarcoidosis Nos	2	0.02	U
Sialoadenitis Nos	2	0.02	U
Skin Hypertrophy	2	0.02	U
Skin Striae	2	0.02	U
Skin Ulcer Nos	2	0.02	U
Sore Throat Nos	2	0.02	U
Splenomegaly	2	0.02	U
Suicidal Ideation	2	0.02	U
Swelling Nos	2	0.02	U

PT	Count of PTs	Percent of Total	Labeled
Tardive Dyskinesia	2	0.02	U
Tenesmus	2	0.02	U
Thrombocytopenia Aggravated	2	0.02	U
Thrombophlebitis Deep	2	0.02	U
Thrombotic Thrombocytopenic Purpura	2	0.02	U
Tooth Abscess	2	0.02	U
Tooth Discolouration	2	0.02	U
Transaminase Nos Increased	2	0.02	U
Trismus	2	0.02	U
Urethritis Non-Specific	2	0.02	U
Vascular Disorder Nos	2	0.02	U
Vascular Purpura	2	0.02	U
Vasospasm	2	0.02	U
Ventricular Arrhythmia Nos	2	0.02	U
White Blood Cell Count Decreased	2	0.02	U
Yawning	2	0.02	U
Abdominal Pain Lower	1	0.01	U
Abortion Nos	1	0.01	U
Adult Respiratory Distress Syndrome	1	0.01	U
Anaemia Folate Deficiency	1	0.01	U
Anaemia Nos Aggravated	1	0.01	U
Anorgasmia	1	0.01	U
Arterial Spasm Nos	1	0.01	U
Aspiration	1	0.01	U
Asthma Aggravated	1	0.01	U
Atelectasis	1	0.01	U
Autoantibody Nos Positive	1	0.01	U
Biliary Colic	1	0.01	U
Biliary Tract Disorder Nos	1	0.01	U
Bilirubinuria	1	0.01	U
Bladder Neoplasm Nos	1	0.01	U
Blindness Nec	1	0.01	U
Blindness Transient	1	0.01	U
Blood Carbon Dioxide Decreased	1	0.01	U
Blood Chloride Increased	1	0.01	U
Blood Culture Positive	1	0.01	U
Blood Glucose Abnormal	1	0.01	U
Blood In Stool	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Blood Iron Decreased	1	0.01	U
Blood Magnesium Decreased	1	0.01	U
Blood Potassium Decreased	1	0.01	U
Blood Pressure Fluctuation	1	0.01	U
Breathing-Related Sleep Disorder	1	0.01	U
Budd Chiari Syndrome	1	0.01	U
Burn Oesophageal	1	0.01	U
Cachexia	1	0.01	U
Cardiac Failure Congestive	1	0.01	U
Cardiomyopathy Nos	1	0.01	U
Central Nervous System Neoplasm Nos	1	0.01	U
Cerebellar Syndrome	1	0.01	U
Cerebral Artery Thrombosis	1	0.01	U
Cerebral Infarction	1	0.01	U
Chemical Poisoning Nos	1	0.01	U
Chest Pressure Sensation	1	0.01	U
Chest Tightness	1	0.01	U
Cheyne-Stokes Respiration	1	0.01	U
Choking	1	0.01	U
Cholestasis	1	0.01	U
Chromosomal Abnormality Nos	1	0.01	U
Chronic Lymphocytic Leukaemia Nos	1	0.01	U
Chronic Myeloid Leukaemia	1	0.01	U
Clamminess	1	0.01	U
Colonic Haemorrhage	1	0.01	U
Complications Of Maternal Exposure To Therapuetic Drugs	1	0.01	U
Congenital Central Nervous System Anomaly Nos	1	0.01	U
Congenital Heart Disease Nos	1	0.01	U
Conversion Disorder	1	0.01	U
Convulsive Threshold Lowered	1	0.01	U
Coombs Negative Haemolytic Anaemia	1	0.01	U
Corneal Opacity	1	0.01	U
Coronary Artery Disease Nos	1	0.01	U
Coronary Artery Occlusion	1	0.01	U
Cow'S Milk Intolerance	1	0.01	U
Cyanosis Peripheral	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Cystitis Haemorrhagic	1	0.01	U
Cytomegalovirus Infection	1	0.01	U
De Toni-Fanconi Syndrome	1	0.01	U
Depressed Mood	1	0.01	U
Diarrhoea Aggravated	1	0.01	U
Difficulty In Walking	1	0.01	U
Disorder Foetal Nos	1	0.01	U
Diverticulitis Nos	1	0.01	U
Diverticulum Intestinal	1	0.01	U
Dry Throat	1	0.01	U
Dysmenorrhoea	1	0.01	U
Echocardiogram Abnormal Nos	1	0.01	U
Eczema Nos	1	0.01	U
Electrocardiogram Qrs Complex Prolonged	1	0.01	U
Electrocardiogram St Segment Abnormal	1	0.01	U
Electrolyte Depletion	1	0.01	U
Emphysema	1	0.01	U
Encephalitis Nos	1	0.01	U
Endocarditis Nos	1	0.01	U
Endometrial Disorder Nos	1	0.01	U
Exacerbation Of Anxiety	1	0.01	U
Excitability	1	0.01	U
Eye Discharge	1	0.01	U
Eye Inflammation Nos	1	0.01	U
Eye Movement Disorder Nos	1	0.01	U
Eyelid Oedema	1	0.01	U
Feeding Disorder Nos	1	0.01	U
Feeding Problem In Newborn	1	0.01	U
Feeling Drunk	1	0.01	U
Frequent Bowel Movements	1	0.01	U
Furuncle (Exc Genital)	1	0.01	U
Gangrene Nos	1	0.01	U
Gasping	1	0.01	U
Gastric Irritation	1	0.01	U
Gastro-Oesophageal Reflux Disease	1	0.01	U
Gastroenteritis Nos	1	0.01	U
Gastrointestinal Pain Nos	1	0.01	U
Gastrointestinal Upset	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Gingival Hyperplasia	1	0.01	U
Glycosuria Present	1	0.01	U
Goitre	1	0.01	U
Gonadotrophin Deficiency	1	0.01	U
Gout Aggravated	1	0.01	U
Growth Retarded	1	0.01	U
Haematocrit Decreased	1	0.01	U
Haemosiderosis	1	0.01	U
Hallucination, Auditory	1	0.01	U
Hearing Impaired	1	0.01	U
Heart Rate Decreased	1	0.01	U
Heat Exhaustion	1	0.01	U
Heat Stroke	1	0.01	U
Hemianopia Nos	1	0.01	U
Hepatic Cyst Nos	1	0.01	U
Hepatic Disorder Nos	1	0.01	U
Hepatic Encephalopathy	1	0.01	U
Hepatitis B Surface Antigen Positive	1	0.01	U
Hiv Infection Nos	1	0.01	U
Hot Flushes Nos	1	0.01	U
Hydrocephalus Nos	1	0.01	U
Hyperbilirubinaemia	1	0.01	U
Hyperchloraemia	1	0.01	U
Hyperphosphataemia	1	0.01	U
Hyperpyrexia	1	0.01	U
Hyperpyrexia Malignant	1	0.01	U
Hyperreflexia	1	0.01	U
Hypogammaglobulinaemia Nos	1	0.01	U
Hypokinesia	1	0.01	U
Hypophosphataemia	1	0.01	U
Influenza	1	0.01	U
Injection Site Inflammation	1	0.01	U
Injection Site Pruritus	1	0.01	U
Insomnia Exacerbated	1	0.01	U
International Normalised Ratio Increased	1	0.01	U
Intracranial Haemorrhage Nos	1	0.01	U
Ischaemic Foot	1	0.01	U
Jerky Movement Nos	1	0.01	U

FDA - Adverse Event Reporting System (AERS)
Standard Report
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Keratitis Nec	1	0.01	U
Lacrimation Increased	1	0.01	U
Large Intestinal Perforation Nos	1	0.01	U
Linear Iga Disease	1	0.01	U
Localised Exfoliation	1	0.01	U
Loin Pain	1	0.01	U
Loss Of Eyelashes	1	0.01	U
Lymphocytosis	1	0.01	U
Lymphopenia	1	0.01	U
Markedly Reduced Food Intake	1	0.01	U
Marrow Hyperplasia	1	0.01	U
Mastitis	1	0.01	U
Megakaryocytes Abnormal	1	0.01	U
Megakaryocytes Increased	1	0.01	U
Meningitis Nos	1	0.01	U
Menorrhagia	1	0.01	U
Mental Retardation Severity Unspecified	1	0.01	U
Migraine Aggravated	1	0.01	U
Monocytosis	1	0.01	U
Mood Swings	1	0.01	U
Multi-Organ Failure	1	0.01	U
Multiple Congenital Abnormalities	1	0.01	U
Multiple Sclerosis	1	0.01	U
Muscle Atrophy	1	0.01	U
Myelitis Nos	1	0.01	U
Nasal Dryness	1	0.01	U
Neuritis Nos	1	0.01	U
Neurological Disorder Nos	1	0.01	U
No Adverse Effect	1	0.01	U
Nodal Arrhythmia	1	0.01	U
Non-Accidental Injury	1	0.01	U
Obesity	1	0.01	U
Oedema Mouth	1	0.01	U
Oesophageal Pain	1	0.01	U
Optic Atrophy	1	0.01	U
Oral Discomfort	1	0.01	U
Oral Soft Tissue Disorder Nos	1	0.01	U
Osteomyelitis Nos	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Osteoporosis Nos	1	0.01	U
Otitis Media Nos	1	0.01	U
Ovarian Cyst	1	0.01	U
Pain Exacerbated	1	0.01	U
Pain In Jaw	1	0.01	U
Pancreatic Disorder Nos	1	0.01	U
Pancreatitis Acute	1	0.01	U
Panic Reaction	1	0.01	U
Parathyroid Disorder Nos	1	0.01	U
Pelvic Pain Nos	1	0.01	U
Pemphigoid	1	0.01	U
Penile Disorder Nos	1	0.01	U
Peripheral Coldness	1	0.01	U
Pharyngeal Oedema	1	0.01	U
Photopsia	1	0.01	U
Pneumothorax Nos	1	0.01	U
Po2 Decreased	1	0.01	U
Polycystic Kidney	1	0.01	U
Polydipsia	1	0.01	U
Posturing	1	0.01	U
Precocious Puberty Nos	1	0.01	U
Proctalgia	1	0.01	U
Productive Cough	1	0.01	U
Protein Urine	1	0.01	U
Prothrombin Time Prolonged	1	0.01	U
Pulmonary Arterial Wedge Pressure Increased	1	0.01	U
Pulmonary Embolism	1	0.01	U
Pulmonary Eosinophilia	1	0.01	U
Pyelonephritis Nos	1	0.01	U
Pyloric Stenosis Nos	1	0.01	U
Quadriplegia	1	0.01	U
Radial Nerve Palsy	1	0.01	U
Rash Pruritic	1	0.01	U
Rash Vesicular	1	0.01	U
Red Eye	1	0.01	U
Renal Colic	1	0.01	U
Renal Disorder Nos	1	0.01	U
Renal Vasculitis	1	0.01	U

FDA - Adverse Event Re[illegible]ng System (AERS)
Standard [illegible]ort
All Preferred Terms in Cases

PT	Count of PTs	Percent of Total	Labeled
Respiratory Distress	1	0.01	U
Restless Leg Syndrome	1	0.01	U
Reticulocyte Count Abnormal	1	0.01	U
Retinal Disorder Nos	1	0.01	U
Retinal Haemorrhage	1	0.01	U
Retinal Vein Thrombosis	1	0.01	U
Retroperitoneal Fibrosis	1	0.01	U
Retroperitoneal Haemorrhage	1	0.01	U
Rhinorrhoea	1	0.01	U
Sarcoma Nos	1	0.01	U
Schizophrenia Nos	1	0.01	U
Scleritis Nos	1	0.01	U
Sensation Of Heaviness	1	0.01	U
Sensation Of Pressure Nos	1	0.01	U
Short-Term Memory Loss	1	0.01	U
Sickness	1	0.01	U
Sinus Tachycardia	1	0.01	U
Skin Atrophy	1	0.01	U
Skin Carcinoma Nos	1	0.01	U
Skin Depigmentation	1	0.01	U
Skin Fungal Infection Nos	1	0.01	U
Sleep Terror	1	0.01	U
Sloughing Of Skin	1	0.01	U
Sneezing	1	0.01	U
Sputum Viscosity Increased	1	0.01	U
Strabismus Nec	1	0.01	U
Stress Symptoms	1	0.01	U
Subcutaneous Nodule	1	0.01	U
Sudden Infant Death Syndrome	1	0.01	U
Superinfection	1	0.01	U
Systemic Lupus Erythematosus Rash	1	0.01	U
Tachyphylaxis	1	0.01	U
Tendon Disorder Nos	1	0.01	U
Tension	1	0.01	U
Tic Nec	1	0.01	U
Tonic Seizures	1	0.01	U
Torsade De Pointes	1	0.01	U
Tourette'S Disorder	1	0.01	U

PT	Count of PTs	Percent of Total	Labeled
Toxicology Nos Abnormal	1	0.01	U
Ulcer Nos	1	0.01	U
Ultrasound Scan Nos Abnormal	1	0.01	U
Umbilical Hernia Nos	1	0.01	U
Upper Respiratory Tract Infection Nos	1	0.01	U
Uraemic Encephalopathy	1	0.01	U
Urethral Pain	1	0.01	U
Urinary Casts	1	0.01	U
Urinary Tract Infection Enterococcal	1	0.01	U
Urine Analysis Abnormal Nos	1	0.01	U
Urine Discolouration	1	0.01	U
Uterine Fibroids	1	0.01	U
Uveitis Nos	1	0.01	U
Vaginal Candidiasis	1	0.01	U
Varicose Veins Nos	1	0.01	U
Vascular Anomaly Nos	1	0.01	U
Venous Thrombosis Deep Limb	1	0.01	U
Ventricular Hypertrophy	1	0.01	U
Weight Gain Poor	1	0.01	U
White Blood Cell Count Increased	1	0.01	U

Attachment O

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CONTAINS NAS TRADE SECRET DATA
FOR FDA INTERNAL USE ONLY
DO NOT RELEASE OUTSIDE FDA

PID# 99274

DATE: AUG 23 1999

FROM: Ann Corken, RPh, MPH, Safety Evaluator
Division of Drug Risk Evaluation II (DDRE II)

THROUGH: Evelyn Rodriguez, M.D., M.P.H., Director
DDRE II, HFD-440

[/S/] for 8/23/99

TO: Lilia Talarico, M.D., Director
Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Consult: Determination of pediatric use for the following drugs: lansoprazole (Prevacid) and omeprazole (Prilosec).

EXECUTIVE SUMMARY:

Gastrointestinal and Coagulation Drug Products, HFD-180, requested pediatric use information for the following drugs: lansoprazole (Prevacid) and omeprazole (Prilosec). Information from the National Disease and Therapeutic Index (NDTI) and the National Prescription Audit (NPA) databases for the years 1997 and 1998 were used to calculate the percentage use in specified pediatric age groups and then the estimated number of prescriptions dispensed.

Information calculated using NDTI data indicated that the percentage use in each age group for lansoprazole and omeprazole was low [redacted]. The percentages for each drug were then combined with the total number of prescriptions dispensed and the total estimated use for combined years 1997 and 1998 in pediatrics is shown below:

1. Omeprazole [redacted] prescriptions
2. Lansoprazole [redacted] prescriptions

INTRODUCTION:

This memorandum is in response to a consult received from HFD-180 requesting information on the pediatric use for the following drugs: lansoprazole (Prevacid) and omeprazole (Prilosec). The information provided will help revise the Pediatric Priority List.

METHODS:

The following formula was used in performing the calculations shown below:

NDTI drug appearances in specified age group/NDTI drug appearances in all age groups X (NPA total Rx dispensed) = Estimated Rx dispensed in specified age group

NDTI = National Disease and Therapeutic Index
NPA = National Prescription Audit
Rx = prescriptions

The numbers were combined for ages 0 to < 1 year and 1 year because appearances were very small in those age groups. We have attached the raw numbers for each drug group by indication for your information. NDTI and NPA data were obtained for the years 1997 and 1998.

RESULTS:

Lansoprazole (Prevacid) (see Attachment A)

Ages 0 to 1 year:
— of total drug appearances were in the age group 0 to 1 year; the estimated prescription use in this age group is — for 1997 through 1998.

Ages 2 to 12 years:
— of total drug appearances were in the age group 2 to 12 years; the estimated prescription use in this age group — for 1997 through 1998.

Ages 13 to 16 years:
— of total drug appearances were in the age group 13 to 16 years; the estimated prescription use in this age group is — for 1997 through 1998.

Total estimate = — prescriptions

Omeprazole (Prilosec) (see Attachment B)

Ages 0 to 1 year:
— of total drug appearances were in the age group 0 to 1 year; the estimated prescription use in this age group is — for 1997 through 1998.

Ages 2 to 12 years:
— of total drug appearances were in the age group 2 to 12 years; the estimated prescription use in this age group is — for 1997 through 1998.

Ages 13 to 16 years:
— of total drug appearances were in the age group 13 to 16 years; the estimated prescription use in this age group is — for 1997 through 1998.

Total estimate = — prescriptions

DISCUSSION/CONCLUSION:

This document describes estimated pediatric use information based on NDTI and NPA databases. NDTI database is a continuing survey designed to provide statistical and demographic information about the patterns and treatment of disease encountered in office-based practice in the U.S. NPA database measures the "retail outflow" of prescriptions, or the rate at which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. One limitation of the NDTI database is that it is a sample-based estimate and thus has the potential for a sampling error.

Information calculated using NDTI data indicated that the percentage use in each age group for lansoprazole and omeprazole was low [redacted]. The percentages for each drug were then combined with the total number of prescriptions dispensed and the total estimated use in pediatrics for the combined years 1997 to 1998 is shown below:

1. Omeprazole— [redacted] prescriptions
2. Lansoprazole— [redacted] prescriptions

[redacted]
Ann Corken, RPh, MPH

Concur:

[redacted]
Toni Piazza-Hepp, Pharm.D., Team Leader

cc:
HFD-180 Goldkind / NDA# 19-810, 20-406
HFD-400 Lillie
HFD-440 Rodriguez/ Chron/ Consult file/ Piazza-Hepp/ Corken
HF-2 Lumpkin

APPEARS THIS WAY
ON ORIGINAL

Attachment P

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PID# 100113

DATE: FEB 11 2000

FROM: Ann Corken, RPh, MPH, Safety Evaluator
Division of Drug Risk Evaluation II (DDRE II)

THROUGH: Evelyn M. Rodriguez, M.D., M.P.H., Director
DDRE II, HFD-440

TO: Lilia Talarico, M.D., Division Director
Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: OPDRA POSTMARKETING SAFETY REVIEW
Drug: Omeprazole (Prilosec)
Reaction: Impotence and Sexual Function Disorders

EXECUTIVE SUMMARY

This memorandum communicates a safety concern identified by OPDRA associated with omeprazole and impotence and sexual function disorders. Given the number of years that omeprazole has been on the market (10 years) and its extensive use, AERS report data suggest that the frequency of impotence associated with omeprazole use is low. However, since impotence appears in the labeling for similar class drugs (lansoprazole and rabeprazole) and documentation was found in the AERS database and in the medical literature, consideration may be given to including impotence in the labeling for omeprazole. It may be premature to consider labeling for other sexual function disorder events discussed in this document based on sporadic numbers of reports.

BACKGROUND

This memorandum communicates a safety concern identified by OPDRA associated with omeprazole and impotence and sexual function disorders.

Omeprazole (Prilosec) is indicated to treat duodenal ulcer and gastric ulcer, symptomatic GERD, erosive esophagitis, and pathological hypersecretory conditions, and for maintanence of healing of erosive esophagitis. It is marketed by Astra Merck and was approved on September 14, 1989. The current labeling contains the following adverse effects related to the genital system in the Adverse Reactions section: testicular pain and gynecomastia.

DRUG USE:

The following table summarizes projected total prescriptions of omeprazole dispensed by retail pharmacies (chain, independent, food store, and mail order) in the U.S. by calendar years 1996 through 1999. **This information is from IMS Health National Prescription Audit Plus (on-line) and is not to be used outside of the FDA without prior clearance by IMS Health.**

	1996	1997	1998	1999	Total
Omeprazole					

METHODS AND RESULTS

Selection of Cases

On December 14, 1999, The Adverse Event Reporting System (AERS) was searched using omeprazole as suspect drug and *Disorders of sexual function and fertility* as the MedDRA HLGT term. The search produced 92 cases (note that it is difficult to determine if any of these reports are duplicates because a majority of the consumer reports were anonymous). Of these 92 reports, 63 cases reported impotence as the primary event and 25 cases reported other sexual-related disorders (decreased fertility and/or sperm count, decreased libido, priapism, retrograde ejaculation, painful erections, and delayed ejaculation). The remaining 4 cases were not included because very little information was provided by the reporter as to the nature of the event.

Summary of Cases

Impotence (n = 63)

DEMOGRAPHIC DATA

AGE:	Range 30 to 82 years (average 52 years) (n = 37)
SEX:	M (61), F (1), UK (1)
REPORTING YEAR:	1991 (1), 1992 (3), 1993 (6), 1994 (3), 1995 (8), 1996 (5), 1997 (6), 1998 (24), 1999 (7)
REPORT LOCATION:	DOMESTIC (62), FOREIGN (1)
REPORTER TYPE:	Health care professional (36), consumer (27)
REACTION ONSET:	1 day to 8 months (average 85 days) (n = 10)
DOSE PER DAY:	20 mg (40), 40 mg (4), UK (19)
DECHALLENGE POSITIVE:	12
RECHALLENGE POSITIVE:	1

Events seen in these cases included (using reporter's terms): difficulty maintaining an erection, exacerbation of impotence, intermittent impotence, impotence, minor impotence, partial impotence, sexual dysfunction, and unable to achieve an erection. In addition to impotence, several patients also reported decreased libido, decreased testosterone levels, gynecomastia, and testicular pain. Impotence and sexual dysfunction were mentioned more frequently than the other events. The following are representative cases:

Case# 3386343 (Mfr# 19981100101) — 1998) A 56-year-old male experienced erectile dysfunction (inability to maintain an erection) after taking 20 mg of omeprazole a day for 1 day to treat esophagitis. The event abated within 2 days of discontinuing omeprazole. Concomitant medications included Pilocar and aspirin.

Case# 5331184 (Mfr# 19950600109) ——reported 1995) A male patient who was older than 50 years experienced impotence ("able to achieve an erection, but not able to sustain it to achieve orgasm") after taking 20 mg of omeprazole a day for an unknown duration. The patient was switched to famotidine; no outcome was reported. He had diabetes mellitus without mention of complication.

Other sexual function disorders (n = 25)

In addition to the reports for impotence described above, other reports of sexual dysfunction were received through AERS. Ten reports of decreased fertility and/or decreased sperm count described the following events: difficulty conceiving (3 reports); oligospermia (2 reports); low sperm count and motility (2 reports); low sperm count (2 reports); and decreased sperm count, testosterone, estrogen, and libido (1 report). Ten reports described a decreased libido (note that 5 of these reports were received from consumers). Five reports described miscellaneous events such as priapism (2 reports), retrograde ejaculation (1 report), painful erections (1 report), and delayed ejaculation (1 report).

Literature Search

As of December 9, 1999 a MEDLINE search of the published English-language literature produced several reports of sexual function disorders associated with the use of omeprazole. Two case reports described impotence and painful nocturnal erections (1, 2). One article (authored by the WHO collaborating Centre) reported case histories for 30 patients receiving omeprazole. Of these 30 patients, 15 patients developed impotence (3 of these patients also developed decreased libido) and 15 patients developed gynecomastia (3). (Note that many reports in the WHO database come from the U.S.; therefore, it is difficult to determine duplication with AERS reports.) Another article reported the results of a questionnaire sent to 86 patients who were receiving omeprazole. A total of 49 patients responded to the questionnaire with 5 patients reporting a difficulty in achieving/maintaining an erection or decreased duration of erection, 4 patients reporting an increase in the frequency of erections, and 2 patients reporting an increase in sex drive (4).

DISCUSSION/CONCLUSION:

This document describes cases of impotence and sexual function disorders possibly associated with the use of omeprazole. Given the number of years that omeprazole has been on the market (10 years) and its extensive use, AERS report data suggest that the frequency of impotence associated with omeprazole use is low. However, since impotence appears in the labeling for similar class drugs (lansoprazole and rabeprazole) and documentation was found in the AERS database and in the medical literature, consideration may be given to including impotence in the labeling for omeprazole, perhaps in the Adverse Reactions section. It may be premature to consider labeling for other sexual function disorder events (decreased fertility and/or decreased sperm count, decreased libido, priapism, retrograde ejaculation, painful erections, and delayed ejaculation) discussed in this document based on sporadic numbers of reports.

REFERENCES:

1. Carvajal A, Martin Arias LH. Gynecomastia and sexual disorders after the administration of omeprazole. Am J Gastroenterol 1995; 90 (6): 1028-9.
2. Dutertre JP, Soutif D, Jonville AP, et al. Sexual disturbances during omeprazole therapy. The Lancet 1991; 338: 1022.
3. Lindquist M, Edwards IR. Endocrine adverse effects of omeprazole. Br Med J 1992; 305: 451-2.
4. Naseer K, Irshad M, Howden CW. Prevalence of male sexual dysfunction during treatment with omeprazole. Gastroenterology 1992; 102: A133.

E /S/ J

Ann Corken, R.Ph., M.P.H.

Concur: E /S/ J

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Team Leader

APPEARS THIS WAY
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Division of Gastrointestinal and Coagulation Drug Products
Medical Officer's Review of Efficacy Studies

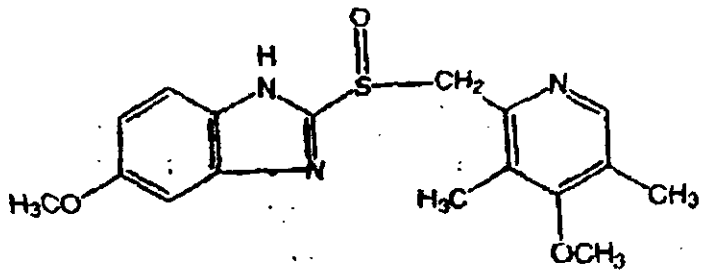
NDA # 21,229

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)

1. **Table of Contents**

2. **Material reviewed:**

a. Initial NDA 21,229 submission dated January 27, 2000 153 volumes
b. Amendments dated March 23, April 14, April 25, April 28, May 19, May 25 and May 30, , July 20, August 2, August 18, September 7, September 20, 2000.

3. Chemistry and manufacturing controls

See appropriate reviews

4. Animal toxicology and toxicology

See appropriate reviews

5. 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 prescription 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). Hydrochloric a5cid 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). Hiatal hernias also tend to promote reflux and HB. 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 are in the range of ¼- 1/8 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 the last dose of a multi-dose treatment period 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 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 meal induced HB prevention is the only type of episode based HB prevention that can be assessed in this submission. No dat has been presented to assess the 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*

Current 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, (nocturnal and daytime) "prevention" of heartburn is the goal of treatment therapy for 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 has not explained how the proposed indication, episodic HB, can be 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 is to become an OTC use. The sponsor discusses the choice of dose in the context of maximal efficacy and acute adverse event profiles, without reference to past precedent.

Reviewer's summary of background points:

1. *The sponsor must clearly define the differences between nonerosive GERD and episodic HB. The lack of physician diagnosis in the past (as proposed in the pivotal studies) is an artificial differentiation (physiologically and medically) 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 HP "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 results 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.*

5.1 Human pharmacology, pharmacokinetics and pharmacodynamics
See biopharmacology review
Several points will be made in this clinical review however, related to proposed dose.

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 1 through 6 and figure 1 (from protocol #129: Astra Merck Inc. submitted January 27, 2000) suggest that there is little difference between 5, 10, and 20 mg of omeprazole in the short term 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

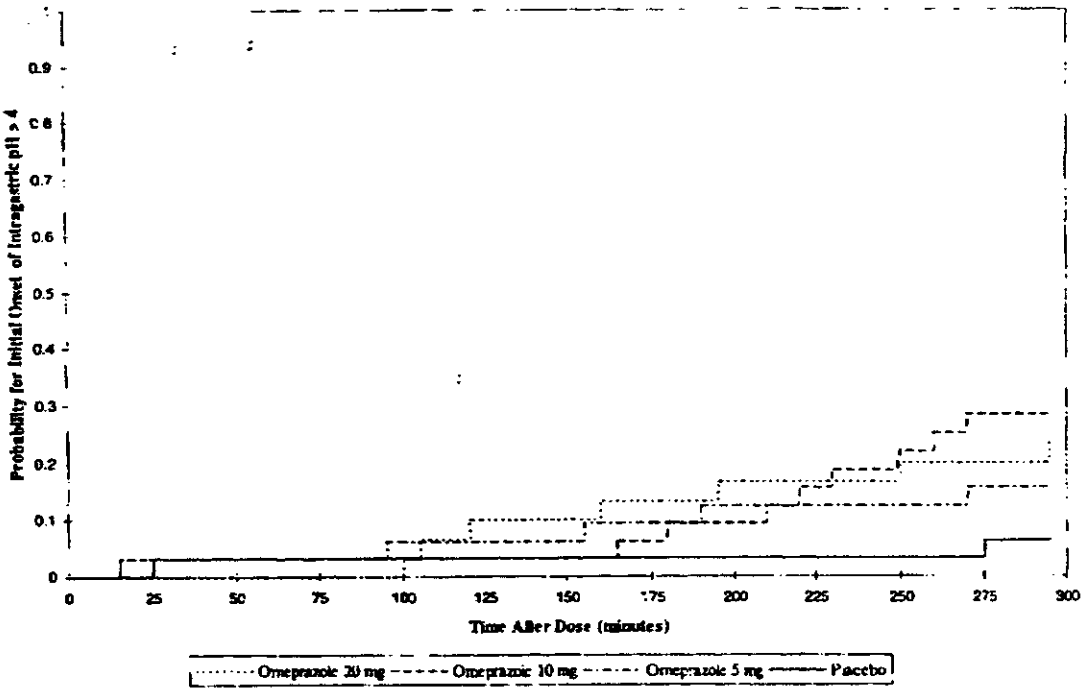
Table 6

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

Kaplan-Meier Estimates* for the Time to Onset of Intragastric pH > 4 by Treatment



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 interval for 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.

6. Description of clinical data sources

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

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

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

7. Clinical Studies

7.1 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.

7.1.1 Trials 092, 095

7.1.1.1 Objective/Rationale

The primary objective of the studies 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"

7.1.1.2 Design

Begin excerpt from sponsor's completed study report (csr) 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:

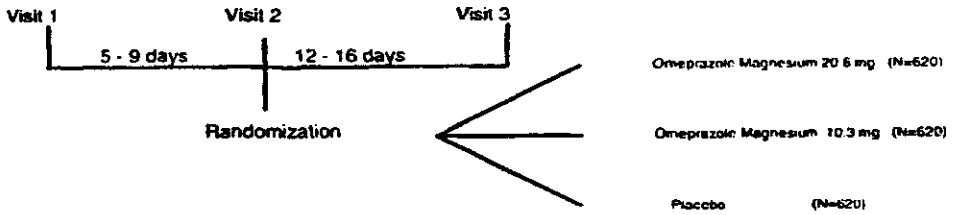
TREATMENT
Ome-Mg 20 (n = 620)
Ome-Mg 10 (n = 620)
Placebo (n = 620)

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[a]	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

[a] Female subjects of child-bearing potential only.

7.1.1.2.1 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.

7.1.1.2.2 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 for a total of 17 secondary endpoints)

Reviewer's Comment:

Efficacy measurements: *The primary endpoint and the first 10 secondary endpoints include analysis of the first episode of HB. 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 provides efficacy if the proposed label is approved. 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 pivotal for approval of OTC HB treatment with the current paradigm of OTC HB therapy. Endpoints for subsequent episodes cannot provide pivotal support for an OTC HB product in the face of potential carry-over effects.

The sponsor cites the basis for approval of Zantac 75 (NDA 20,520) in 1995 to indicate that sustained relief has been used as the basis of approval of an OTC product. 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) demonstrated therapeutic gain(displayed below) for endpoints similar to the current sponsor. 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 OM for HB treatment. 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. Results of studies 092 and 095 are not comparable in their totality to the Zantac submission. Referenced by the current sponsor.

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.

7.1.1.3 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 performed.

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.

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. 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 11

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 demonstrates 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.*

Evaluation and treatment of GERD related symptoms vary in current medical practice.

Indications and timing of endoscopy in patients with HB 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.

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 OM. The effects of recent prior doses (doses within the prior 72 hours) on the results of current dose cannot be prevented or controlled.*

The division requested a sensitivity analysis of all treated episodes separated from recent prior treatment. Although this reviewer feels that first dose efficacy is critical, hypothesis generating analyses of all treated episodes separated adequately from pharmacodynamic carry- over effects may be of interest. These results are discussed in the results section.

Table 12

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.

7.1.2.2 Efficacy Results:

First Treated Episode Results

Table 13

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.

Table 14

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	**75.6%[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:

The primary endpoint is stringent and has not been chosen by past sponsors as the primary endpoint for the approval of heartburn treatment. However it is the most valuable and clinically relevant to the patient.

1. *There was no trend in either study for the primary endpoint for the **first treated episode**. 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 influence subsequent episode results in OM studies more profoundly than such effects would in studies of short acting OTC products.*

2. *Table 14 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.*

The Division requested additional analyses of treated episodes of HB separated by at least 2- 4 days from previously treated episodes. These analyses were submitted in September 2000. These analyses were requested to improve the understanding of the all treated episodes analysis as presented by the sponsor. These results reinforce the lack of efficacy seen in the first treated episode analysis.

Table 15

Percent of treated episodes with indicated outcome HB episodes that were separated by at least 4 days from any previously treated episode (ITT subjects from studies 092 and 095)

Outcome	*Study*	*20 mg*	*10 mg*	*Placebo*
Sustained complete relief	*092*	*31.2*	*32.9*	*29.9*
	095	*30.2*	*30.5*	*29.0*
Complete relief within one hour	*092*	*33.3*	*35.7*	*32.3*
	095	*33.3*	*33.7*	*30.8*
Sustained adequate relief	*092*	*64.5*	*66.7*	*63.5*
	095	*69.1**	*64.8*	*59.9*
Adequate relief within one hour	*092*	*72.5*	*75.2*	*72.3*
	095	*75.7**	*73.2**	*67.6*
Backup medication (Gelusil) use	*092*	*8.4*	*8.4*	*10.5*
	095	*7.5**	*8.4*	*11.2*
Overall assessment of study medication	*092*	*53.7*	*56.9**	*51.2*
	095	*57.7*	*54.9**	*47.1*

**** Indicates that the sponsor defined the paired treatment comparison to have a p-value of <0.05 obtained from the generalized equation analysis. Given the post hoc nature of this analysis and multiplicity of comparisons, statistical meaning is difficult to assess. The reviewer displays the analysis for qualitative analysis only.***

Table 16

Percent of treated episodes with indicated outcome: HB episodes that were separated by at least 2 days from any previously treated episode (ITT subjects from studies 092 and 095)

Outcome	Study	20 mg	10 mg	Placebo
Sustained complete relief	092	33.4	32.3	30.1
	095	31.4	30.0	29.3
Complete relief within one hour	092	35.3	34.6	32.3
	095	33.7	33.1	30.9
Sustained adequate relief	092	65.8	65.9	63.7
	095	70.3	64.3	60.5
Adequate relief within 1st hour	092	73.9	73.7	72.3
	095	76.9	72.8	68.3
Backup medication use	092	8.8	9.0	11.7
	095	7.8	9.0	11.0
Overall assessment of study medication	092	55.8	57.0	51.4
	095	58.7	54.7	47.7

Last Treated Episode Efficacy

Table 17

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	0.080	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 18 reveals a 6-10% therapeutic gain that is statistically significant for the complete sustained relief within one hour for the last treated episode.

Table 18

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 19

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.

Reviewer's Comment:

1. *Table19 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 21 and 22. The average treatment frequency was 7 out of 14 days. The pharmacodynamic profile of OM strongly suggests a substantial carry-over effect from previous doses contributed to 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.*

Table 21 (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: Tt9981/ home1/ts6801/1997092/saspgm/extexp.sas
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Table 22 (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.

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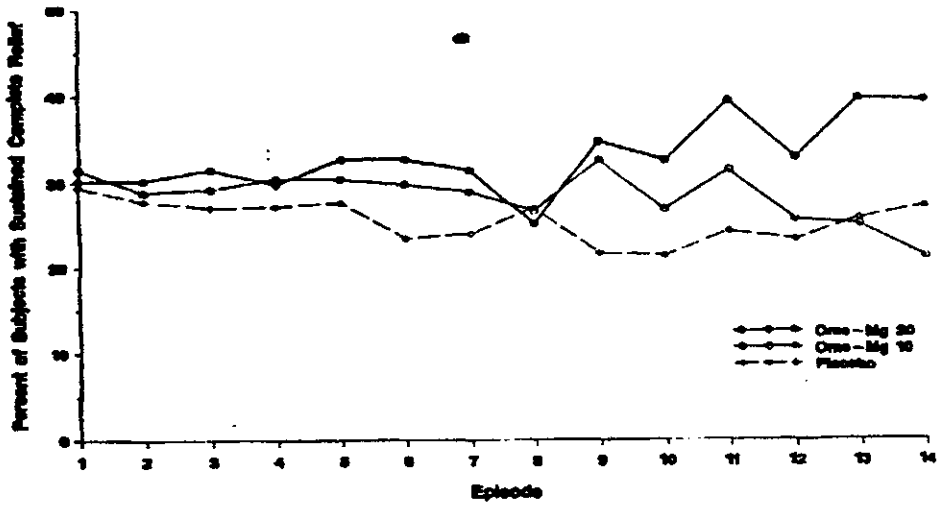
Figure 2

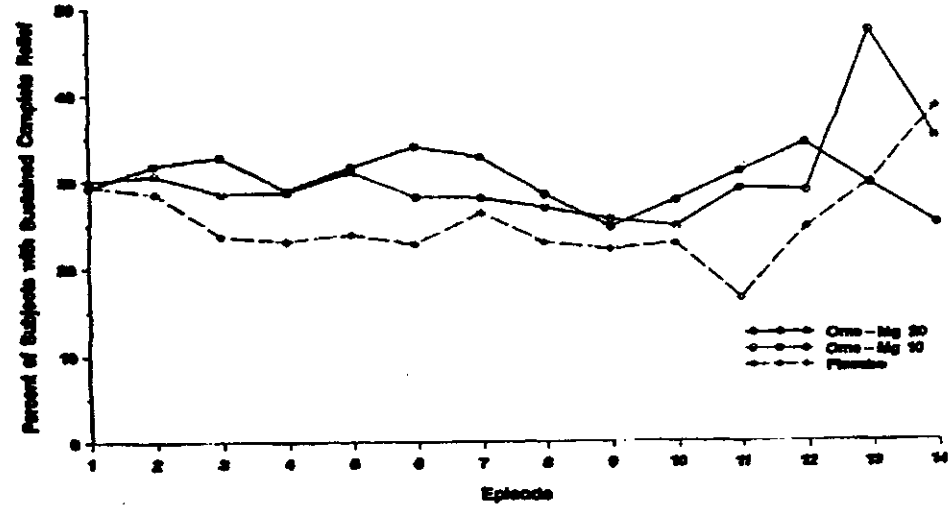
FIGURE 6
TREATMENT OF HEARTBURN SYMPTOM STUDIES
PERCENTAGE OF SUBJECTS WITH SUSTAINED COMPLETE RELIEF BY EPISODE
INTENT-TO-TREAT SUBJECTS

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:

Figure 2 provides a valuable 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 in study 092. 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 as noted earlier in this review. If carry 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

First HB episode

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 among 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

It is unclear how one may correct for the multiplicity of endpoints studied in these trials. Therefore even these inconsistent "statistically significant" finding may not truly be statistically significant.

Additional HB studies

The sponsor conducted three additional studies of OM for HB relief in 1999; 017, 018 and 019. The design was similar to that used in HB treatment trials submitted in other previously approved OTC HB treatment applications. The design of 017 involved single use at home and 018 and 019 involved treating single episodes of meal provoked HB in-clinic. The results were submitted to the IND 54,307, but not to the NDA. The reader is referred to these submissions. Four endpoints were studied:

1. ***Sustained complete relief***
2. ***Sustained adequate relief***
3. ***Overall assessment of study medication***
4. ***Backup medication use***

The sponsor's conclusions were that all three of these studies failed to detect a difference between either dose of OM and placebo in the treatment of acute episodes of HB. Over 11000 subjects were enrolled in these trials.

The failure to show a trend in favor of OM for the primary endpoint combined with the inconsistent results for secondary endpoints and failure at all studied endpoints in other submitted studies precludes approval of OM for the treatment of occasional, episodic HB based on this submission.

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 may reflect a carry-over effect from prior doses.

All treated episodes

1. *There appears to be marginal benefit at best 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. Clinically small 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.

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.

Table 23

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 24

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 23 and 24 indicate that in subjects with mild HB, OM trended worse than placebo. This represents the most appropriate population for OTC HB treatment. This finding casts further doubt on the value of OM for the treatment of occasional HB 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.

In summary: Adequate and well controlled studies have failed to demonstrate efficacy for OM 10 or 20 mg in the management of single episodes of occasional or episodic HB.

7.1 Indication #2: Prevention of Meal induced HB

7.2.1 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 [redacted]
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 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 mg versus OM 20 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 multicenter, 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, ——— , 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

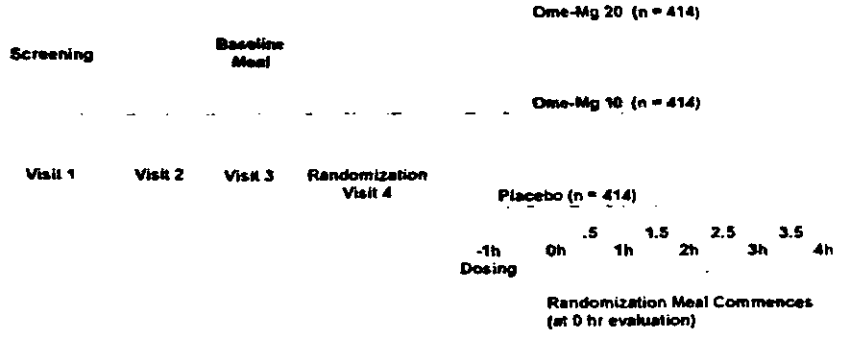


Table 25

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 25 (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
Geluxil 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.

7.2.1.2 Results:

Demographics: Tables 26-29 display the disposition and demographics of the three groups in both studies.

Table 26

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 27

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%	78.3%	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%	3.3%	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%	1.6%	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.

Table 28

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%)	398 (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 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 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	12.93	13.34	13.55	13.30
Minimum–Maximum	18–78	18–86	18–81	18–86	18–93	19–80	18–81	18–93
< 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 30

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	29.8%	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 31

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 acute efficacy of OM on HB other than meal induced HB in the provocative meal setting. Overall prevention (HB of any cause) in the 2-week prevention model is possible is analyzed properly.

Efficacy results:

Table 32

8.7 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 8.2.1, 8.2.2, 8.2.3, and 8.2.16 in Clinical Study Reports 1998005 and 1998006 for the table results. See Appendix 1.1.2 of Section 8.7 for documentation of these table results.

Reviewer's Comment:

Results of studies 005 and 006 are displayed in tables32, 33, and 34. These data reflect a modest but statistically significant benefit for OM 10 or 20mg for total prevention of HB in study 006 and a smaller statistically insignificant numeric benefit in study 005 that is of questionable clinical relevance. 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 33

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: TT9981 /home3/tj4346/ise056/saspgm/logisl.sas, mergecmh.sas, hb_free.sas
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Secondary efficacy endpoints

Table 34

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	0.56
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 suggests that there may be a small measurable preventive effect of OM 20-mg in the setting of a single provocative meal. These results are displayed in table 34. 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 34 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.

Choice of proper dose will need to be addressed once the efficacy and OTC appropriateness of this product are considered together. There is precedent for approving OTC HB treatment only at a fraction of the prescription level.

Stratification by baseline history of factors contributing to HB

Table 35 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 35

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%	8.4%	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%	113/468	24.1%	4.8%	77/400	19.3%
No	102/414	24.6%	5.4%	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.
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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 36

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.
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The data in table 36 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.

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. Support for the claim of prevention of meal induced episodic HB includes:*
   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*

In view of the failure of OM to treat episodic HB, the two reviewing divisions will need to decide whether it is appropriate to allow OTC HB prevention for episodic HB without concomitant efficacy at treatment. Certainly, inappropriate off label usage for treatment can be expected with OM when all other approved products are labeled for both indications. Consumer confusion is anticipated. This reviewer feels that marketing for episodic prevention without some efficacy at treatment is not consistent with consumer and many physicians' understanding of these indications. Creating a new subcategory of acute HB management OTC to accommodate this sponsor's limited efficacy is not recommended.

7.2 Indication #3

7.3.1"24 hour 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 <u>not related to a specific meal</u>. 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. Despite this intention, there is a very fine 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 24-hour prevention of HB is indistinguishable from GERD treatment. OTC treatment of GERD is not currently approved. <u>Efficacy</u> 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. The appropriateness of this new OTC indication must first be assessed before the efficacy becomes a relevant subject for review. These issues include:

- ***masking more serious conditions***
- ***delays in accurate diagnosis of conditions that require other than OTC acid reduction therapy***
- ***undertreating severe forms of GERD***
- **consumer ability to correctly follow instructions for a new treatment regimen for OTC HB**
- **long term effects of chronic acid suppression in a large segment of the population**

Nonetheless, the efficacy of OM in this setting will be reviewed.

7.2.2 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:

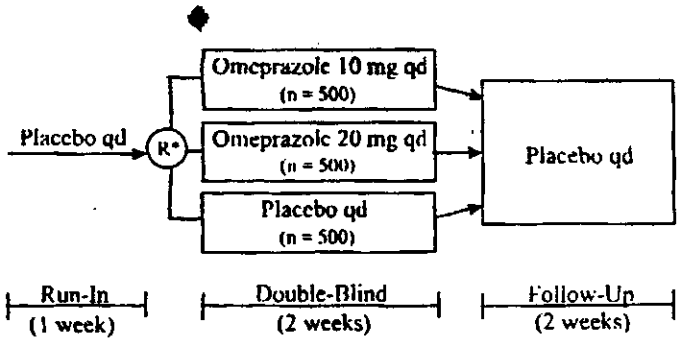
- Single-Blind placebo Run-In (one week),
- Double-Blind randomized treatment (two weeks), and
- Single-Blind placebo Follow-Up (two weeks).

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. *The indication of 24-hour prevention is a new concept for OTC HB management. Again, before considering efficacy data, the agency must first decide whether this indication falls within the episodic HB category or GERD management category. The proposed 10-day treatment period does not meet current medical practice guidelines for empiric treatment of presumptive GERD. Current practice algorithms suggest 4-6 weeks of treatment. For episodic HB treatment/prevention, currently labeled OTC products limit usage to 14 days continuously. The design of this study represents a hybrid of the current management of reflux symptoms through the use of OTC medications and the current medical practice of the management of GERD for a fraction of the current standard of treatment duration.*
2. *Inclusion/Exclusion Criteria:*

a. *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.*

b. *Excluding subjects with a diagnosis of GERD, while including subjects who have been on antisecretory drugs including prescription strength H2Ras and PPIs in the past is inconsistent. This suggests that ,indeed subjects with GERD who have been treated for GERD by their physicians are included.*

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

7.3.3 Results:

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

Subject disposition:

Table 37

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 38

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 (97.8%)	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 39

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	19–86	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%	19.8%	18.1%	18.7%	18.9%	18.7%	20.4%	19.8%	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 indicate 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 40

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 41

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 42

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	0.008	1.40 (1.09, 1.79)	8.2% (2.2, 14.2)

STUDY 183	Ome-Mg 20	Ome-Mg 10	PLACEBO
Heartburn-Free (%)	46.8% (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 43

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 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 44

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 45

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. It is also unclear what the treatment duration should be.

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 progressively decreasing 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 for such a short period of time 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 46

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

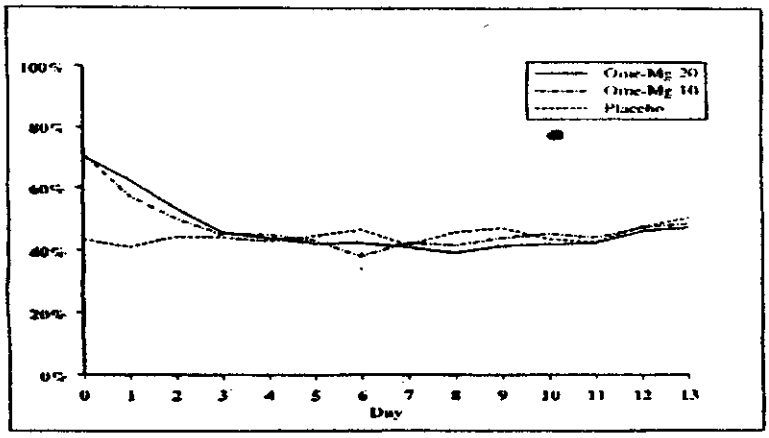
	50th Percentile[a]		75th Percentile[a]	
	171	183	171	183
Ome-Mg 20	3	3	5	5
Ome-Mg 10	2	3	4	5
Placebo	1	1	3	3

[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.

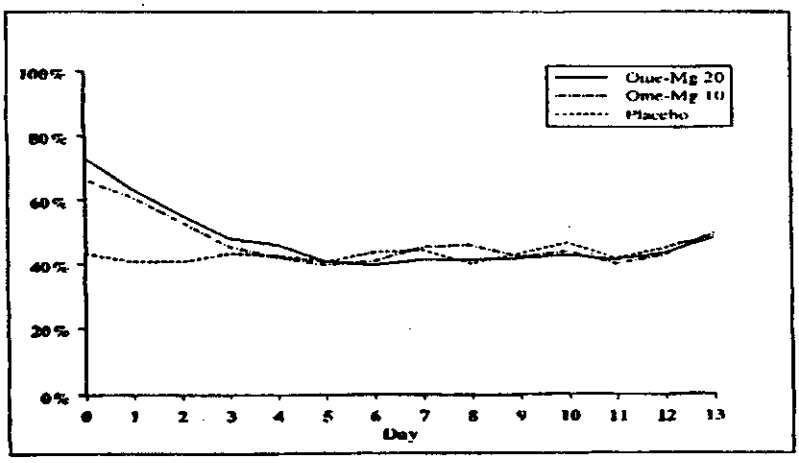
Figure 3

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

Study 171



Study 183



* Note: Day 0 is last evaluation of double-blind medication.

Table 46 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 of HB for a meaningful period of time then it may obviate the need for evaluation by a physician. If, as expected, 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 warnings for the need for medical evaluation. The sponsor's assertion that the proposed label addresses a truly episodic symptomatic condition is not consistent with:

1. *the common medical understanding of heartburn chronicity*
2. *the pharmacodynamics of OM*
3. *the demographic composition of the study population*
4. *the results from the treatment period*
5. *the rapid recurrence of symptoms in the study population.*
6. *Results of the usage studies to be discussed in the review by the Division of OTC Drugs.*

A potential concern with the use of potent acid suppressive agents is rebound acid 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 does however suggest that rebound acid hypersecretion would not 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.

Subgroup Analysis:

Table 47

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	18.9	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.

Table 47 (cont)

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 48

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 49

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	171/454	37.7	5.2	145/446	32.5
No	278/557	49.9	17.7	279/584	47.8	15.6	191/593	32.2
Stress and/or Anxiety								
Yes	335/713	47.0	13.7	284/699	40.6	7.3	235/705	33.3
No	170/334	50.9	20.7	166/339	49.0	18.7	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	142/295	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	38/128	29.7
No	452/941	48.0	15.3	392/927	42.3	9.6	298/911	32.7
Lying Down								
Yes	311/658	47.3	16.7	264/649	40.7	10.1	198/648	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 47 reveals some variations in the magnitude of trend but no reverse trends. Interestingly, similar to the results of studies 005 and 006 (table 36; 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 require further evaluation if consistently seen across submissions related to omeprazole. A review of databases should be requested of the sponsor to address this finding.*
2. *The difference in efficacy seen between subjects with <50% and those with ≥ 50% of days with HB during run-in is of note (see table 47). If the majority of the efficacy is in the treatment of more frequent sufferers of HB (GERD), the true current OTC target population may in fact experience no therapeutic benefit if the trend seen in this subanalysis were to be prospectively studied.*
3. *Table 49 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. The design of such studies would require discussion between the Division and the sponsor.

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

1. **Studies 171 and 183 represent replicated evidence of efficacy of OM for the prevention of HB over a 14-day period.**
2. **The efficacy as defined by the therapeutic gain over placebo treatment increase over the course of the 14 days of treatment**
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.**
4. **This indication is not currently part of the OTC label for HB management. There are broad implications of labeling an OTC product for 24-hour prevention for up to 10 days. Such labeling more clearly relates to GERD than a single episode of HB.**

8 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:

1. 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

i. 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
ii. statistically significant superiority of OM 20 mg versus placebo in both studies for five secondary endpoints: overall assessment, maximum severity score, backup medication use within 4 hours, average symptom score and reduction of maximum severity score. The issue of multiplicity corrections has not been addressed.

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)

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

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%)

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

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 without 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.

Recommendations for regulatory action:

1. Prilosec 1 should not be approved as proposed by the sponsor.
2. HB beyond the occasional isolated episode is primarily a symptom of chronic GERD. OTC use of a product labeled to provide 24-hour prevention of symptoms for multidose periods will be concentrated in a large population of people currently defined medically as chronic GERD sufferers. These people are currently primarily on chronic therapy under a physicians supervision with therapy initiated following a medical evaluation.
   The Division should convene a panel of medical experts, both in primary care and gastroenterology to give guidance on the impact on current medical practice and safety of treating the chronic HB symptoms of GERD OTC long term.
3. If chronic management of GERD is approved conceptually by the Agency as an OTC indication, labeling should take into account the absence of acute efficacy of this product and the need for multi-dose treatment for adequate clinical efficacy.
4. Labeling comprehension and usage studies would then be required to assess the ability of an OTC label to adequately guide consumers in a current OTC setting where acute treatment is desired and available with other approved products but not with Prilosec 1.
5. The sponsor should be asked to address the apparent differences in efficacy observed between Caucasians and non-Caucasians in this submission. Analysis of data from related studies in previous NDAs should be included.
6. These recommendations should be viewed in the context of the separate safety review and OTC currently under final draft.

Lawrence Goldkind, M.D.

cc:
NDA 21-229
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/LGoldkind
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/s/

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	21-229
Sponsor:	Astra-Zeneca LP Wayne, PA
Date Submitted:	January 27, 2000
Drug:	Omeprazole Magnesium (Prilosec 1™) for OTC use
Pharmacological Category:	Proton Pump Inhibitor; inhibitor of gastric acid secretion
Formulation:	20 mg tablets
Administration:	The sponsor proposes that one over-the-counter oral tablet be administered for the relief of heartburn, acid indigestion and sour stomach or for the prevention of these symptoms brought on by consuming food and beverages or associated with events such as stress, hectic life style, lying down for exercise, once every 24 hours for no more than 10 days in a row, unless directed by a doctor.
Material Reviewed:	Application, clinical sections, labeling, summary, safety update report, case report tabulations, case report forms, other pertinent information and literature references
Reviewer:	Mark Avigan, M.D., C.M.

Brief Summary of Key Safety Issues Identified in this Review

This clinical safety review is based primarily on data gathered from the following sources: A. 10 US clinical trials involving 11,299 subjects to study Omeprazole-Mg for OTC use; B. 6 US and 29 non-US trials consisting of 5,757 unique patients treated for GERD, erosive esophagitis and dyspepsia with 10mg, 20 mg or 40mg daily doses of the prescription formulation of omeprazole. Duration of drug exposure ranged between one day to 12 weeks (short-term studies) and up to one year (long-term studies); C. A database of Voluntary Reports of World-wide serious adverse events and US non-serious adverse events associated with omeprazole exposure since 1989. The database includes 15,385 reports, includes 287 deaths and 1,750 non-fatal serious adverse events (not necessarily causally related to the drug).

Based on the following observations it is likely that consumers will use the OTC Omeprazole-Mg either chronically or intermittently: First, the proposed labeling does not warn against long-term intermittent use. Second, a significant number of test subjects continued to treat themselves beyond the 10-day upper limit. Third, a single dose has little acid neuralizing benefit and multiple doses are required to achieve maximal suppression. Fourth, a significant number of individuals recruited into the studies and in an OTC setting have chronic heartburn consistent with GERD. This condition is characterized by a high rate of recurrence of symptoms. In this review, two categories of AEs have been analyzed. A. AEs related to short-term drug exposure (12 weeks or less); B. AEs related to long-term exposure (more than 12 weeks).

Short-term drug exposure can be linked in a small percentage of patients with the following AEs. Although rare, OTC consumers should be warned by adequate labeling to recognize them and if necessary seek medical attention. Rare AEs include:

1. A range of liver toxicities.--These are usually mild, idiosyncratic and reversible upon drug withdrawal. However, the drug has very rarely been linked to significant liver damage and even death. Causality of significant omeprazole-induced hepatitis has been confirmed in some cases by rechallenge with the drug.
1. Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome - although very rare, some cases have been linked to death.
1. Agranulocytosis and other forms of Bone Marrow suppression - these are rare events are usually, but not always, reversible.
1. Urticaria/skin rashes.--The incidence of skin hypersensitivity responses may be as high as 0.5 per 1000 exposed individuals.
1. Anaphylaxis/angioedema.--Although the incidence has not been determined, cases of severe systemic hypersensitivity responses to the drug have been confirmed by drug rechallenge.

Special populations in the OTC market are subjects of special concern. They include:

1. Pediatric subjects for who the prescription formulation has not been FDA approved. The clinical study and post-marketing safety databases for individuals under the age of 18 are very small. At this time OTC approval in this age group is not warranted.

1. Pregnancy - Omeprazole is categorized as a 'Class C' drug because of embryo-fetal toxicity in some animal models as well as its association with certain genotoxic effects. On the other hand, extensive human off-label exposure has not revealed drug-induced loss of fertility or teratogenicity. Further studies are required to exclude the possibility that this drug has an affect (possibly rare) on the outcome of some pregnancies.

1. Drug-Drug interactions - In addition to effects on the absorption of certain anti-fungal drugs omeprazole has the potential to reduce clearance of drugs that are metabolized by CYP2C19, such as diazepam, phenytoin and R-warfarin. Exaggerated effects in the presence of multiple drug usage or background disease of the liver or other organs has not been excluded in some individuals. The absence of a learned intermediary requires informative labeling that recommends non-usage by susceptible individuals and early recognition of side-effects in relevant populations.

Long-term exposure of omeprazole (more than 12 weeks and in some cases more than 1 year) has been linked linkage to the following:

1. Masking of diseases such as advanced stages of erosive esophagitis, Barrett's esophagus, esophageal epithelial dysplasia, esophageal cancer and gastric cancer - Temporary amelioration of symptoms may lead to critical delays in the seeking of attention by a physician. Advise from an expert panel concerning the benchmarks of safety for OTC access of Proton Pump Inhibitors (including omeprazole) should be sought prior to consideration of approval of omeprazole for use by self-medicating consumers.

1. Prolonged hypergastrinemia and genotoxic potential - Drug-induced hypergastrinemia may be pronounced in some people with H. Pylori infection, 'slow-metabolizers' and other population subsets. Although an association of omeprazole exposure in undifferentiated users with tumor formation has not emerged, prospective or nested case control studies of large numbers of treated individuals should be pursued.

1. Rebound of Acid Secretion - Continuous usage of omeprazole longer than 1 month has been linked to significant rates of acid rebound upon cessation of treatment. The relationship between this phenomenon and usage patterns should be elucidated.

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Therefore, it is not suprising that a single standard dose of omeprazole only partially suppresses acid secretion[1] . On a theoretical basis, it is difficult to predict the precise rate of change of intragastric pH with repeated doses of omeprazole. Nonetheless, to achieve a target 3.0 for at least 16 to 18 hours per 24 hour period, at least two or three days duration of daily omeprazole treatment with a standard dose is required[2]. Within 24 hours after the first dose of omeprazole it is predicted that the intragastric pH will be elevated beyond 3.0 less than 50% of the time. Since the drug is no longer present at a significant concentration in blood beyond 5-6 hours after its administration, in order to improve acid control after maximal inhibition is achieved, it is more appropriate to increase dose frequency rather than the amount per dose. Although it has been postulated that an optimal target for healing of duodenal ulcer disease is a pH greater than 3.0 for 16 to 18 hours per 24 hour period a threshold target for the consistent symptomatic alleviation of heartburn in the US population has not been established. Nonetheless, it is likely that to consistently eradicate heartburn patients with GERD and/or recurrent symptoms it is necessary to achieve a pH consistently higher than 3.0 during the periods between meals and at nighttime. Thus, it would not be surprising if maximal alleviation of heartburn in some individuals in response to once daily administration of standard doses of a PPI would only be achieved after two or three days. The pharmacological niche of PPIs as preventers of heartburn, rather than as agents which rapidly alleviate heartburn after a single dose must be taken into account in analyzing the future usage pattern of this drug. Based on the pharmacodynamic properties of omeprazole it is predictable that a significant percentage of individuals will self-medicate with this drug on a chronic continuous or intermittent basis. The potential for such a pattern of usage must be taken into account in the formulation of analysis of its safety profile.

LABELING REQUESTED

The sponsor has requested OTC approval for omeprazole mg 20.6 mg, 1 tablet per day, for both the relief and prevention of heartburn. The proposed labeling includes the following instructions:

- Do not use for more than ——— in a row unless directed by a doctor
- Do not use if you are allergic to omeprazole
- Do not use with if you have difficulty swallowing
- Do not use with ———
- Stop use and ask a doctor if stomach pain ←————→
- Ask a doctor or pharmacist before use if you are taking ketoconazole or itraconazole - both antifungal medicines

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[1] T Lind, et al. Effect of omeprazole - a gastric proton pump inhibitor - on pentagastrin stimulated acid secretion in man. Gut 1983; 24:270-276.
D Castell. An Open Label, Single Center, Famotidine Controlled Single Dose Cross Over Study to Evaluate the Effects of Omeprazole on Acid Suppression in Heartburn Patients by Measuring Intragastric and Intra-esophageal pH. Synopsis

[2] G Sachs et al. The Pharmacology of the Gastric Acid Pump: The H^+,K^+ ATPase. Annu Rev Pharmacol Toxicol. 1995; 35:277-305

- If pregnant or breast-feeding, ask a health professional before use. ———
- Children ——— of age: ask a doctor

The following conditions/situations are not addressed in the proposed labeling:

- Whether individuals with chronic heartburn should use OTC omeprazole on an intermittent basis which in the aggregate last weeks or months, before seeking consultation with a physician
- Whether patients with multiple symptoms such as heartburn and abdominal pain should use the OTC formulation
- Whether patients with known upper GI pathological conditions should use the OTC formulation
- Whether females of reproductive age should use birth control methods in conjunction with the OTC formulation to prevent pregnancy
- Whether the OTC formulation should be used when experiencing unusual symptoms associated with heartburn, such as exercise related discomfort
- The duration of time in the beginning of a treatment course when one should expect relief of heartburn symptoms

CLINICAL STUDY SAFETY RESULTS PRIMARY SAFETY DATA BASE

In the submission, adverse event information has been provided from the following sources:

- 10 US clinical trials involving 11, 299 subjects to study Omeprazole-magnesium (Ome-Mg) tablets for OTC use. These studies form the core of the current NDA submission and were a significant component of the safety database. A total of 8,179 subjects in these studies were exposed to Ome-Mg from one dose to multiple doses given over a 4 week period. In the database, 5,040 subjects were exposed to 20 mg doses of Ome-Mg and 3,039 subjects to 10 mg doses of Ome-Mg. In addition, 3,120 subjects were exposed to placebo.
- A database of previous clinical trials to study the prescription formulation of omeprazole for the treatment of GERD, erosive esophagitis and dyspepsia. 6 US trials, 29 non-US trials consisting of over 7,500 patients (5,757 unique patients) treated with omeprazole comprised this database. In these clinical trials patients were treated with doses of 10 mg, 20mg or 40 mg with a duration of exposure ranging from one day to 12 weeks (short-term studies) and up to one year (long-term studies; 1,235 patients).
- A database of voluntary reports at AstraZeneca LP (SafeTnet) of serious adverse events (SAEs), during the ——— courses of prescription treatment and nonserious adverse events (AEs) in the US from a background of ——— courses of treatment since 1989. The database includes 15,385 AE reports from 7,344 patient cases and includes 287 outcomes of death. It also contains 1,750 cases of nonfatal SAEs.

Determination of the safety profile of this drug can conveniently be divided into 2 categories:

- An analysis of adverse events related to short-term drug administration (less than 12 weeks) characterized by a single course of treatment without chronic or intermittent use
- An analysis of adverse events related to long-term drug administration (more than 12 weeks) characterized by chronic or intermittent use

The sponsor has made a presentation to support the claim that omeprazole-mg has a benign safety profile in the context of short-term use (10 day limit). Despite this assumption, a thorough safety analysis must take the following points into consideration:

- The proposed labeling does not specifically warn against long-term intermittent use
- Actual Use studies of the product indicate that a significant percentage of test subjects who were self-medicated to prevent heartburn, did not follow instructions in the label and continued to treat themselves beyond 10 days
- The pharmacodynamic/pharmacokinetic characteristics of omeprazole include the points that maximal acid suppression does not occur after a single 20 mg dose, but only occurs after 2-3 days with daily dosaging. Moreover, the effects, even of a single dose, last for up to 5 days. These properties are consistent with a high degree of efficacy for the prevention of chronic heartburn rather than occasional episodes of heartburn that, in the absence of an ongoing treatment course, require immediate relief by the administration of a single tablet
- A significant percentage of subjects who were recruited into the OTC studies had chronic heartburn consistent with GERD. The natural course of GERD is characterized by a high percentage of individuals who develop recurrence of symptoms when treatment to suppress gastric acid is stopped

For these reasons, it is likely that many consumers will use the OTC product, either chronically or intermittently. Safety issues that are related to short-term and long-term omeprazole-mg exposure, as defined above, will be addressed separately (Parts A and B, respectively), followed by conclusions (Part C).

ADVERSE EVENTS ASSOCIATED WITH SHORT-TERM ADMINISTRATION OF OMEPRAZOLE (LESS THAN 12 WEEKS TOTAL USE)

OTC Ome-Mg Clinical Trial Adverse Events

A total of 10 US studies involving 11,299 subjects have contributed to the safety database (see Table 1). 8,179 subjects were exposed to Ome-Mg from a single dose to 4 weeks of active treatment. Of these, 5,040 were treated with 20 mg doses and 3,039 subjects were treated with 10 mg doses. The composite number of individuals treated with placebo alone was 3,120.

TABLE 1
LISTING OF PROTOCOLS INCLUDED IN THE OMEPRAZOLE OTC SUMMARY
(PAGE 1 OF 2)

PROTOCOL NUMBER	US/NON	TYPE OF STUDY	TREATMENT[a]	DURATION OF TREATMENT	TOTAL NUMBER OF SUBJECTS EVALUATED FOR SAFETY	STUDY DESIGN[b]
171	US	24-hr prevention of heartburn	Ome-Mg 10, Ome-Mg 20, Placebo	1 wk plbo. run-in, 2 wk treatment, 2 wk plbo follow-up	527 528 526	Multi-center, DB, randomized, double-dummy, parallel, plbo-cont.
183	US	24-hr prevention of heartburn	Ome-Mg 10, Ome-Mg 20, Placebo	1 wk plbo. run-in, 2 wk treatment, 2 wk plbo follow-up	526 525 525	Multi-center, DB, randomized, double-dummy, parallel, plbo-cont.
1998005	US	preprandial prevention of heartburn	Ome-Mg 10, Ome-Mg 20, Placebo	single dose	430 433 423	Multi-center, DB, randomized, double-dummy, parallel, plbo-cont.
1998006	US	preprandial prevention of heartburn	Ome-Mg 10, Ome-Mg 20, Placebo	single dose	387 394 390	Multi-center, DB, randomized, double-dummy, parallel, plbo-cont.
1997092	US	treatment of heartburn	Ome-Mg 10, Ome-Mg 20, Placebo	1 wk plbo. run-in, 2 wk treatment	636 628 635	Multi-center, DB, randomized, double-dummy. parallel, plbo-cont.
1997095	US	treatment of heartburn	Ome-Mg 10, Ome-Mg 20, Placebo	1 wk plbo. run-in, 2 wk treatment	633 638 621	Multi-center, DB, randomized, double-dummy, parallel, plbo-cont.

[a] Ome-Mg 10 represents omeprazole magnesium tablets 10.3 mg; Ome-Mg 20 represents omeprazole magnesium tablets 20.6 mg; OME 20 represents omeprazole 20 mg capsules.

[b] DB = double blind; SB = single blind; plbo-cont = placebo controlled.

TABLE 1 (CONTINUED)
LISTING OF PROTOCOLS INCLUDED IN THE OMEPRAZOLE OTC SUMMARY
(PAGE 2 OF 2)

PROTOCOL NUMBER	US/NON	TYPE OF STUDY	TREATMENT[a]	DURATION OF TREATMENT	TOTAL NUMBER OF SUBJECTS EVALUATED FOR SAFETY	STUDY DESIGN[b]
1998003	US	Actual Use	Ome-Mg 20	4 wks	833	Multi-center, multi-dose, open-label, at-home use
1998067	US	Adolescent Actual Use	Ome-Mg 20	4 wks	92	Multi-center, multi-dose, open-label, at-home use
1998014	US	Actual Use/Forecast market volume	Ome-Mg 20	4 wks	939	Multi-center, multi-dose, open-label, at-home use
200	US	Relative Bioavailability	Ome-Mg 10 x2, Ome-Mg 20, OME 20	single dose; 5-day washout between visits	30[c] 29 29	Single-center, randomized, open-label, 3-way cross-over

[a] Ome-Mg 10 represents omeprazole magnesium tablets 10.3 mg; Ome-Mg 20 represents omeprazole magnesium tablets 20.6 mg; OME 20 represents omeprazole 20 mg capsules.

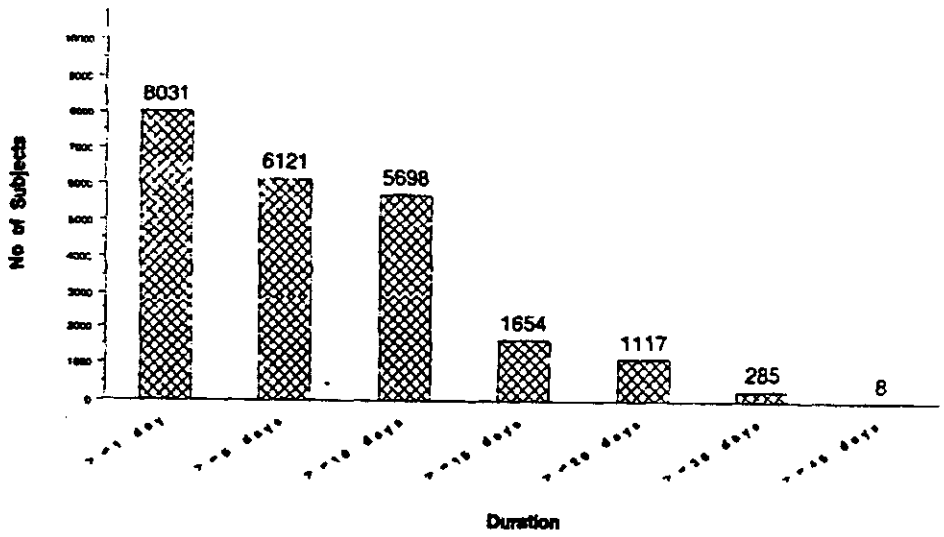
[b] DB = double blind; SB = single blind; plbo-cont = placebo controlled.

[c] 30 subjects were included in the safety analysis set. Adverse events were collected during each period and combined across the two Ome-Mg treatments.

As shown in Figure 2 it should be noted that in this cluster of studies:

- Patients were not treated for longer than 4 weeks
- Approximately 5;500 subjects were administered omeprazole for 10 days or longer
- Approximately 1,000 subjects were administered omeprazole for 20 days or longer
- Approximately 300 subjects were administered omeprazole for 30 days or longer
- 8 subjects were administered omeprazole for more than 45 days

Study medication safety was evaluated from the self-reported AEs experienced by subjects during the course of treatment with drug and for various short periods of time prior to and after cessation of treatment, depending on the particular protocol attached to each study.



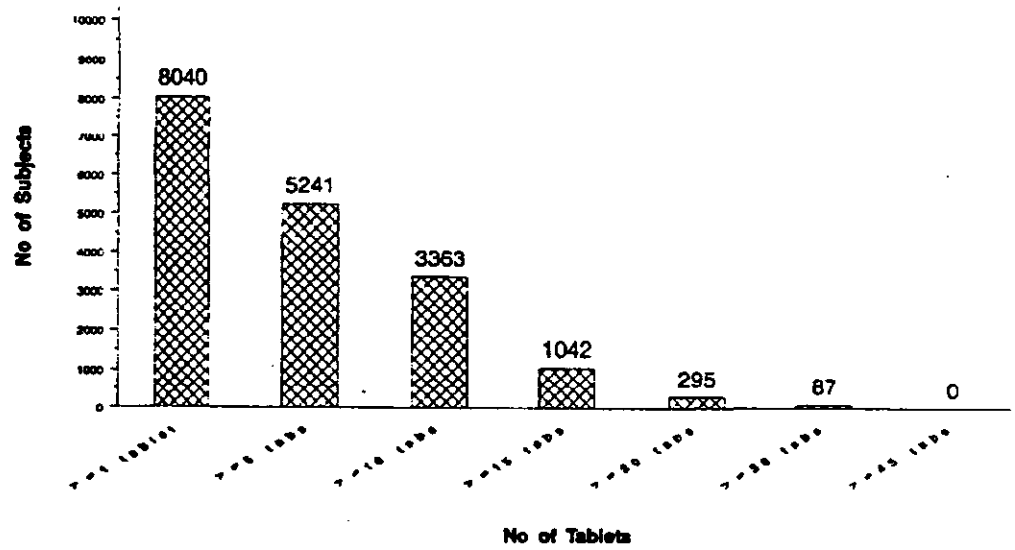
1) Ome-Mg(Omeprazole Magnesium) treatment includes both 10.3mg and 20.6mg
2) Duration based on Days of Usage (number of days between first date and last date)
3) Includes Subjects from the following studies :
P&G 1997092, 1997095, 1008003, 1008006, 1998006, 1998014, 1998087,
AMI 171, 183, 200 (Only includes data from period where latest formulation was taken)

Fig. 2 - OTC Extent of Exposure: Summary of OTC Subjects Exposed to Ome-Mg by Duration of Treatment

- In all studies AEs were scored during the active phase of treatment. In some they were also recorded during a brief placebo run-in period and/or a brief post-treatment followup period. AEs were recorded during the indicated study phases.

- 1 week placebo 'run-in' phase, 2 week 'double-blind' treatment phase and 2 week placebo 'follow-up' phase in Studies 171 and 183.
- 48 hour period after drug administration and meal provocative test in studies 1998005 and 1998006.
- Period including 5 - 9 day placebo run-in phase, 12 - 16 day treatment phase and 7 day follow-up period after the last dose of medication in studies 1997092 and 1997095.
- 4 week actual use evaluation period with voluntary reporting of AEs in studies 1998003, 1998067 and 1998014.
- Period encompassing 3 single doses of Ome-Mg or omeprazole with 5 day wash-out periods between visits in Study 200.

In these studies, the limited exposure to omeprazole is further demonstrated by a tabulation of the distribution in the number of tablets taken by study subject (see Figure 3).



1) Ome-Mg(Omeprazole Magnesium) treatment includes both 10.3mg and 20.6mg.
2) Includes Subjects from the following studies :
P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067,
AMI 171, 183, 200 (Only includes data from period where tablet formulation was taken)

Fig. 3 - OTC Extent of Exposure: Summary of OTC Subjects Exposed to Ome-Mg by Number of Tablets Taken

It is apparent that the entire safety analysis presented represents very short-term and limited exposure to the drug as well as short-term monitoring of AEs. A drawback for the detection of rare AEs is the limited number of patients who have been entered into the OTC studies.

Because of the spectre that the OTC formulation of Ome-Mg will be used by large numbers of consumers either continuously or intermittently for extended periods of time, a safety analysis of longer term exposure to the prescription formulation of this drug derived both from previously performed studies as well as post-marketing surveillance has been presented. It is important to consider that there may be differences in population based susceptibilities to side effects related to omeprazole between a patient population prescribed thjis drug and self-medicating consumers. This issue will be discussed further below.

A demographic breakdown of OTC study entrants shown in Table 2 demonstrates that the majority of individuals who received either Ome-Mg or placebo were Caucasian (82%) and between the ages of 18 and 64 (89%). Gender breakdown revealed that females were more highly represented than males (56% vs 44%). Although African Americans represented 12% of study entrants there was smaller representation by Hispanics (4%) and minimal representation by Asians (1%). It should be pointed out that in the Caucasian population approximately 3% of individuals express a polymorphic isoform of CYP2C19 that is associated with a reduction in the metabolism of omeprazole. These 'poor metabolizers' (PMs) who are deficient in CYP2C19 activity demonstrate drug plasma concentration and AUCs after a standard dose of omeprazole that are approximately 5-fold or higher than individuals who are 'rapid-metabolizers' (RMs). The plasma elimination half-life of omeprazole in PMs is approximately 3-fold longer than in RMs. The PM polymorphism occurs in a higher proportion of Asians (15%) of Japanese, Chinese and Korean origin. Drawing firm conclusions about susceptibility to drug toxicity in this group based on empirical data from these studies is not possible because of their low representation. With regards to age of study entrants there is a very low representation of adolescents (12-17 years of age) but an approximate 10% representation of geriatric subjects (65 years of age or older). Although the reduction of liver clearance of omeprazole in the elderly is relatively modest (the AUC is approximately two-fold higher than in younger subjects) it is important to determine that certain individuals in this age group is not vunerable to toxicity by omeprazole.

Integrated Summary of Safety

TABLE 2
DEMOGRAPHIC DATA FOR Ome-Mg[a] AND PLACEBO OTC SUBJECTS[b]
SUMMARY BY PARAMETER,
CATEGORY AND TREATMENT GROUP

PARAMETER	Ome-Mg (N = 8179)[c]		PLACEBO (N = 3120)[c]		OVERALL (N = 11299)[c]	
CATEGORY	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Gender						
Female	4623	57%	1715	55%	6338	56%
Male	3556	43%	1405	45%	4961	44%
Overall	8179	100%	3120	100%	11299	100%
Age (Years)						
12–17	105	1%	0	0%	105	1%
18–64	7196	88%	2858	92%	10054	89%
≥ 65	873	11%	262	8%	1135	10%
Unknown	5	<1%[f]	0	0%	5	<1%[f]
Overall	8179	100%	3120	100%	11299	100%
Race						
Asian	48	1%	21	1%	69	1%
Black	961	12%	376	12%	1337	12%
Caucasian	6686	82%	2560	82%	9246	82%
Hispanic	361	4%	139	4%	500	4%
Indian (American)	37	<1%[f]	7	<1%[f]	44	<1%[f]
Multi-Racial	86	1%	17	1%	103	1%
Overall	8179	100%	3120	100%	11299	100%

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.

[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).

[c] Number of subjects evaluable for safety.

[d] Number of subjects within specified Parameter, Treatment Group, and Category.

[e] Percent of subjects within specified Parameter, Treatment Group, and Category: (n/N)*100.

[f] Percentage <0.5% are reported as <1%.

Source TJ4346: /home3/tj4346/ss/saspgm/tab3.sas 10-Sep-98

In a composite of the OTC studies 19% of the 8,179 subjects who were treated with Ome-Mg and 14% of the 3,120 subjects who were treated with placebo reported one or more AEs. Table 3 lists the incidence of the most commonly reported AEs in descending order of incidence down to 1% for the active drug and placebo.

Integrated Summary of Safety

TABLE 3
ADVERSE EVENTS FOR Ome-Mg[a] AND PLACEBO OTC SUBJECTS[b]
SUMMARY BY COSTART AND TREATMENT
DESCENDING TO ONE PERCENT

	Ome-Mg (N = 8179)[c]		Placebo (N = 3120)[c]		Overall (N = 11299)[c]	
COSTART Term	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Overall	1530	19%	442	14%	1972	17%
HEADACHE	439	5%	109	3%	548	5%
INFECT	190	2%	62	2%	252	2%
DIARRHEA	167	2%	56	2%	223	2%
PAIN ABDO	115	1%	29	1%	144	1%
NAUSEA	112	1%	30	1%	142	1%
FLATUL	88	1%	14	<1%[f]	102	1%
PAIN	72	1%	10	<1%[f]	82	1%
PAIN BACK	70	1%	16	1%	86	1%
FLU SYND	63	1%	13	<1%[f]	76	1%
DYSPEPSIA	54	1%	9	<1%[f]	63	1%
PHARYNGITIS	49	1%	12	<1%[f]	61	1%
VOMIT	45	1%	18	1%	63	1%
DIZZINESS	42	1%	8	<1%[f]	50	<1%[f]

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.

[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).

[c] Number of subjects evaluable for safety.

[d] Number of subjects who reported adverse events within specified Treatment Group and COSTART.

[e] Percent of subjects who reported adverse events within specified Treatment Group and COSTART: (n/N)*100.

[f] Percentage <0.5% are reported as <1%.

Descending to one percent as determined by the Ome-Mg column.

See Appendix Table 1 for more details.
Source TJ4346: /home3/tj4346/iss/sasppgm/tab5.sas 10-Sep-99

The most commonly reported AEs were headache (5%), infection (2%) and diarrhea (2%). These rates do not appear to be significantly higher than the rates observed in individuals treated with placebo. Similarly, in a 465 patient US clinical trial of the prescription delayed-release capsule formulation of omeprazole, headache and diarrhea were considered to be possibly/probably/definitely related to the drug in 2.4% and 1.9% of study patients, respectively[3]. In conjunction with skin rash which was observed in 1.1% of patients in the clinical study population, these side-effects were generally mild and self-limiting.

Upon analysis of the incidence of headache associated with Ome-Mg, by gender the incidence higher in females (6% active drug vs 3% placebo) compared to males (4%

[3] Physicians Desk Reference, 1999

active drug vs 4% placebo). Differences by gender of other common side-effects were not apparent (see Table 4).

Integrated Summary of Safety

TABLE 4
ADVERSE EVENTS FOR Ome-Mg[a] AND PLACEBO OTC SUBJECTS[b]
SUMMARY BY GENDER, COSTART, AND TREATMENT
DESCENDING TO ONE PERCENT
(PAGE 1 OF 2)

	Ome-Mg				Placebo			
	Female (N = 4623)[c]		Male (N = 3556)[c]		Female (N = 1715)[c]		Male (N = 1405)[c]	
COSTART Term	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Overall	951	21%	579	16%	250	15%	192	14%
HEADACHE	285	6%	154	4%	56	3%	53	4%
INFECT	116	3%	74	2%	44	3%	18	1%
DIARRHEA	102	2%	65	2%	31	2%	25	2%
NAUSEA	87	2%	25	1%	21	1%	9	1%
PAIN ABDO	82	2%	33	1%	20	1%	9	1%
FLATUL	57	1%	31	1%	9	1%	5	<1%[f]
PAIN	50	1%	22	1%	7	<1%[f]	3	<1%[f]
PAIN BACK	43	1%	27	1%	9	1%	7	<1%[f]
FLU SYND	39	1%	24	1%	8	<1%[f]	5	<1%[f]
CONSTIP	30	1%	10	<1%[f]	5	<1%[f]	4	<1%[f]
PHARYNGITIS	30	1%	19	1%	8	<1%[f]	4	<1%[f]
SINUSITIS	29	1%	11	<1%[f]	6	<1%[f]	6	<1%[f]
DYSPEPSIA	28	1%	26	1%	5	<1%[f]	4	<1%[f]
VOMIT	27	1%	18	1%	11	1%	7	<1%[f]
COUGH INC	25	1%	6	<1%[f]	4	<1%[f]	3	<1%[f]
DIZZINESS	24	1%	18	1%	4	<1%[f]	4	<1%[f]
RHINITIS	22	<1%[f]	18	1%	6	<1%[f]	8	1%

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.

[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).

[c] Number of subjects evaluable for safety.

[d] Number of subjects who reported adverse events within specified Gender, COSTART, and Treatment Group.

[e] Percent of subjects who reported adverse events within specified Gender, COSTART, and Treatment Group: (n/N)*100.

[f] Percentage <0.5% are reported as <1%.

Descending to one percent as determined by the Ome-Mg Female column.

Source TJ4346: /home3/tj4346/iss/saspgm/tab7.sas 10-Sep-99

No age-related differences in AEs between geriatric and younger age subjects were observed (see Table 5).

Integrated Summary of Safety

TABLE 5
ADVERSE EVENTS FOR Ome-Mg® OTC SUBJECTS[b]
SUMMARY BY AGE AND COSTART
DESCENDING TO ONE PERCENT (PAGE 1 OF 2)

	12–17 (N = 105)[c]		18–64 (N = 7196)[c]		≥ 65 (N = 873)[c]		UNKNOWN (N = 5)[c]		OVERALL (N = 8179)[c]	
COSTART TERM	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Overall	53	50%	1303	18%	171	20%	3	60%	1530	19%
HEADACHE	12	11%	386	5%	39	4%	2	40%	439	5%
INFECT	20	19%	150	2%	19	2%	1	20%	190	2%
DIARRHEA	1	1%	141	2%	25	3%	0	0%	167	2%
NAUSEA	2	2%	103	1%	7	1%	0	0%	112	1%
PAIN ABDO	5	5%	92	1%	18	2%	0	0%	115	1%
FLATUL	0	0%	74	1%	14	2%	0	0%	88	1%
PAIN	3	3%	62	1%	7	1%	0	0%	72	1%
PAIN BACK	2	2%	60	1%	8	1%	0	0%	70	1%
FLU SYND	6	6%	49	1%	8	1%	0	0%	63	1%
DYSPEPSIA	3	3%	44	1%	7	1%	0	0%	54	1%

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TABLE 5 (continued)
ADVERSE EVENTS FOR Ome-Mg® OTC SUBJECTS[b]
SUMMARY BY AGE AND COSTART
DESCENDING TO ONE PERCENT
(PAGE 2 OF 2)

	12–17 (N = 105)[c]		18–64 (N = 7189)[c]		≥65 (N = 872)[c]		UNKNOWN (N = 5)[c]		OVERALL (N = 8171)[c]	
COSTART TERM	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
VOMIT	0	0%	43	1%	2	<1%[f]	0	0%	45	1%
PHARYNGITIS	6	6%	39	1%	4	<1%[f]	0	0%	49	1%
SINUSITIS	0	0%	38	1%	2	<1%[f]	0	0%	40	<1%[f]

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.
[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).
[c] Number of subjects within specified Age category.
[d] Number of subjects who reported adverse events within specified Age and COSTART.
[e] Percent of subjects who reported adverse events within specified Age and COSTART: (n/N)*100.
[f] Percentage <0.5% are reported as <1%.

Descending to one percent as determined by the 18–64 years of age column.
Source TJ4346 /home3/tj4346/ss/saspgm/tab11.sas 10-Sep-99

The higher percentage of adolescent subjects (12-17 years old age group) reporting one or more AEs probably reflects the fact that this age group was only studies in open-label trials of 4 weeks duration without placebo (Studies 067 and 003).

The assessment of omeprazole related side-effects in adolescents is limited by the following:

- In the composite of OTC studies only 105 subjects were in this age group. This small number precludes detection of side-effects that may be age-related.

- Currently the prescription formulation of omeprazole is only approved by the FDA for adult use. This reflects absence of adequate studies to determine efficacy/safety profiles in pediatric individuals, including adolescents (see below).

- World-wide post-marketing surveillance of both SAEs and non-serious AEs in children ages 12-16 captured in SafeTNet (see below) contains a total of 92 AEs experienced by 39 unique patients. This small number precludes an assessment of the repertoire of side-effects that may be associated with omeprazole in adolescents, particularly those that are uncommon.

- As shown in Table 6 it is apparent that AEs associated with the cardiovascular system were more frequent in the 12-17 age group (6%) than in other age groups. The side-effects observed in adolescents in Studies 067 and 003 were predominantly marked by episodes of migraine headaches or vasodilation. In these studies there was no placebo control arm.

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TABLE 6
ADVERSE EVENTS FOR Ome-Mg® OTC SUBJECTS[b]
SUMMARY BY AGE AND BODY SYSTEM
(PAGE 1 OF 2)

	12–17 (N = 186)[c]		18–64 (N = 7186)[c]		≥ 65 (N = 873)[c]		UNKNOWN (N = 5)[c]		OVERALL (N = 8179)[c]	
BODY SYSTEM	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Body as a Whole	31	30%	587	8%	72	8%	2	40%	692	8%
Cardiovascular System	6	6%	24	<1%[f]	7	1%	0	0%	37	<1%[f]
Digestive System	12	11%	473	7%	70	8%	0	0%	555	7%
Endocrine System	0	0%	2	<1%[f]	0	0%	0	0%	2	<1%[f]
Hemic and Lymphatic System	0	0%	8	<1%[f]	6	1%	0	0%	14	<1%[f]
Metabolic and Nutritional Disorders	0	0%	24	<1%[f]	4	<1%[f]	0	0%	28	<1%[f]
Musculo-Skeletal System	3	3%	70	1%	10	1%	0	0%	83	1%
Nervous System	1	1%	81	1%	14	2%	0	0%	96	1%
Respiratory System	22	21%	270	4%	33	4%	1	20%	326	4%

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TABLE 6 (continued)
ADVERSE EVENTS FOR Ome-Mg® OTC SUBJECTS[b]
SUMMARY BY AGE AND BODY SYSTEM
(PAGE 2 OF 2)

	12–17 (N = 186)[c]		18–64 (N = 7186)[c]		≥ 65 (N = 873)[c]		UNKNOWN (N = 5)[c]		OVERALL (N = 8179)[c]	
BODY SYSTEM	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Skin and Appendages	1	1%	45	1%	11	1%	0	0%	57	1%
Special Senses	1	1%	24	<1%[f]	3	<1%[f]	0	0%	28	<1%[f]
Urogenital	2	2%	42	1%	4	<1%[f]	0	0%	48	1%
Total Number of Subjects with One or More AEs	53	50%	1303	18%	171	20%	3	60%	1530	19%

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.
[b] Includes subjects from the following studies: P&G 1997082, 1997095, 1998003, 1998005, 1998006, 1998014, 1998057, AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).
[c] Number of subjects within specified Age category.
[d] Number of subjects who reported adverse events within specified Age and Body System
[e] Percent of subjects who reported adverse events within specified Age and Body System: (n/N)*100.
[f] Percentage <0.5% are reported as <1%.
Source TJ4346 /home3/tj4346ss/sasprgm/tab6.sas 10-Sep-99

Table 7 displays the most commonly reported AEs associated with Ome-Mg across all racial groupings:

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TABLE 7
ADVERSE EVENTS FOR Ome-Mg[a] OTC SUBJECTS[b]
SUMMARY BY RACE AND COSTART
DESCENDING TO ONE PERCENT (PAGE 1 OF 2)

COSTART Term	Black (N = 961)[c]		Caucasian (N = 6686)[c]		Hispanic (N = 361)[c]		Other (N = 171)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Overall	113	12%	1318	20%	64	18%	35	20%
HEADACHE	33	3%	383	6%	11	3%	12	7%
INFECT	17	2%	165	2%	3	1%	5	3%
DIARRHEA	14	1%	144	2%	7	2%	2	1%
PAIN ABDO	5	1%	106	2%	2	1%	2	1%
NAUSEA	12	1%	96	1%	3	1%	1	1%
FLATUL	8	1%	74	1%	4	1%	2	1%
PAIN	4	<1%[f]	65	1%	2	1%	1	1%
PAIN BACK	8	1%	56	1%	2	1%	4	2%
FLU SYND	4	<1%[f]	52	1%	5	1%	2	1%

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TABLE 7 (continued)
ADVERSE EVENTS FOR Ome-Mg[a] OTC SUBJECTS[b]
SUMMARY BY RACE AND COSTART
DESCENDING TO ONE PERCENT
(PAGE 2 OF 2)

COSTART Term	Black (N = 961)[c]		Caucasian (N = 6686)[c]		Hispanic (N = 361)[c]		Other (N = 171)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
PHARYNGITIS	0	0%	47	1%	2	1%	0	0%
DYSPEPSIA	2	<1%[f]	46	1%	2	1%	4	2%
DIZZINESS	2	<1%[f]	38	1%	2	1%	0	0%
VOMIT	4	<1%[f]	37	1%	2	1%	2	1%
RHINITIS	2	<1%[f]	36	1%	2	1%	0	0%
CONSTIP	2	<1%[f]	34	1%	3	1%	1	1%

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.
[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998008, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).
[c] Number of subjects within specified Race category.
[d] Number of subjects who reported adverse events within specified Race and COSTART.
[e] Percent of subjects who reported adverse events within specified Race and COSTART: (n/N)*100.
[f] Percentage <0.5% are reported as <1%.

Descending to one percent as determined by the Caucasian column.
Source TJ4346: /home3/tj4346/tss/sasppm/tab14.sas 10-Sep-99

In the composite of OTC studies a total of 961 Blacks, 361 Hispanics and 171 others complemented the 6,686 Caucasians who made up the subject population. It should be noted that representation by Asians, particularly of Japanese, Chinese and Korean extraction was minimal. From the data, there is no evidence that common side effects are predisposed to occur in particular racial groups. Because of the relatively high representation of 'slow-metabolizers' of omeprazole in people of Asian origin compared

to Caucasians (15% vs 3%) a definitive assessment of AE rates in Asians is currently not possible.

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TABLE 8
ADVERSE EVENTS FOR Ome-Mg[a] AND PLACEBO OTC SUBJECTS IN *CONTROLLED* STUDIES[b]
SUMMARY BY COSTART AND TREATMENT
DESCENDING TO ONE PERCENT

	Ome-Mg 20 (N =3146)[c]		Ome-Mg 10 (N = 3139)[c]		PLACEBO (N = 3120)[c]	
COSTART TERM	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Overall	470	15%	475	15%	442	14%
HEADACHE	102	3%	87	3%	109	3%
DIARRHEA	54	2%	59	2%	56	2%
INFECT	51	2%	53	2%	62	2%
NAUSEA	36	1%	43	1%	30	1%
PAIN ABDO	35	1%	22	1%	29	1%
FLATUL	22	1%	27	1%	14	<1%[f]
PAIN BACK	21	1%	19	1%	16	1%
VOMIT	19	1%	21	1%	18	1%
PHARYNGITIS	19	1%	15	<1%[f]	12	<1%[f]
FLU SYND	17	1%	19	1%	13	<1%[f]
RHINITIS	17	1%	12	<1%[f]	14	<1%[f]
DYSPEPSIA	16	1%	10	<1%[f]	9	<1%[f]
PAIN	16	1%	16	1%	10	<1%[f]

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.
[b] Includes subjects from the following placebo-controlled studies: P&G 1997092, 1997095, 1998005, 1998006; AMI 171, 183.
[c] Number of subjects evaluable for safety.
[d] Number of subjects who reported adverse events within specified Treatment Group and COSTART.
[e] Percent of subjects who reported adverse events within specified Treatment Group and COSTART: (n/N)*100.
[f] Percentage <0.5% are reported as <1%.

Descending to one percent as determined by the Ome-Mg column.
Source TJ4346: /home3/tj4346/ss/sasprgm/tab16.sas 10-Sep-99

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In Table 8 incidence of commonly reported AEs during double-blind placebo controlled trials is shown. It is apparent that the profile of Ome-Mg 20 mg daily doses is similar to the profile of 10 mg doses. This finding is consistent with the sponsor's interpretation that there are no dose-related differences of AEs in this dose range. However, it should be emphasized that within the set of the 6 clinical controlled OTC studies numbers of study subjects were too small to assess dose-related risks of rare/very rare AEs. Furthermore, long-term expsorue to varying doses to Ome-Mg was not performed.

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TABLE 9
Ome-Mg[a] AND PLACEBO OTC SUBJECTS[b]
SUMMARY OF SUBJECTS DISCONTINUED DUE TO ADVERSE EVENTS
DURING ACTIVE TREATMENT OR PLACEBO FOLLOW-UP PHASES
(PAGE 1 OF 4)

	Ome-Mg (N = 8179)[c]		PLACEBO (N = 3120)[c]		OVERALL (N = 11299)[c]	
COSTART Term	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Overall	41	1%	18	1%	59	1%
NAUSEA	9	<1%[f]	3	<1%[f]	12	<1%[f]
HEADACHE	8	<1%[f]	2	<1%[f]	10	<1%[f]
VOMIT	8	<1%[f]	2	<1%[f]	10	<1%[f]
DIARRHEA	5	<1%[f]	4	<1%[f]	9	<1%[f]
PAIN ABDO	5	<1%[f]	3	<1%[f]	8	<1%[f]
DIZZINESS	4	<1%[f]	0	0%	4	<1%[f]
PAIN CHEST	3	<1%[f]	0	0%	3	<1%[f]
RASH	3	<1%[f]	1	<1%[f]	4	<1%[f]
ASTHENIA	2	<1%[f]	0	0%	2	<1%[f]
COLITIS	2	<1%[f]	0	0%	2	<1%[f]
DYSPEPSIA	2	<1%[f]	0	0%	2	<1%[f]
DYSPNEA	2	<1%[f]	0	0%	2	<1%[f]
FEVER	2	<1%[f]	0	0%	2	<1%[f]
PAIN BACK	2	<1%[f]	0	0%	2	<1%[f]
ANGINA PECTORIS	1	<1%[f]	0	0%	1	<1%[f]
ARTERIOSCLEROSIS	1	<1%[f]	0	0%	1	<1%[f]
CARCINOMA	1	<1%[f]	0	0%	1	<1%[f]
CHILLS	1	<1%[f]	0	0%	1	<1%[f]
CONSTIP	1	<1%[f]	1	<1%[f]	2	<1%[f]
DEATH	1	<1%[f]	0	0%	1	<1%[f]
DELUSIONS	1	<1%[f]	0	0%	1	<1%[f]
EDEMA	1	<1%[f]	0	0%	1	<1%[f]
EDEMA LARYNX	1	<1%[f]	0	0%	1	<1%[f]
FLATUL	1	<1%[f]	1	<1%[f]	2	<1%[f]
GI DIS	1	<1%[f]	1	<1%[f]	2	<1%[f]
HYPERTENS	1	<1%[f]	1	<1%[f]	2	<1%[f]
INFARCT MYOCARD	1	<1%[f]	0	0%	1	<1%[f]
INJURY ACCID	1	<1%[f]	0	0%	1	<1%[f]
KIDNEY CALCULUS	1	<1%[f]	0	0%	1	<1%[f]

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TABLE 9 (continued)
Ome-Mg[a] AND PLACEBO OTC SUBJECTS[b]
SUMMARY OF SUBJECTS DISCONTINUED DUE TO ADVERSE EVENTS
DURING ACTIVE TREATMENT OR PLACEBO FOLLOW-UP PHASES
(PAGE 3 OF 4)

COSTART TERM	Ome-Mg (N = 8179)[c]		PLACEBO (N = 3120)[c]		OVERALL (N = 11299)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
MENINGITIS	1	<1%[f]	0	0%	1	<1%[f]
MYALGIA	1	<1%[f]	0	0%	1	<1%[f]
PAIN EYE	1	<1%[f]	0	0%	1	<1%[f]
PARESTHESIA	1	<1%[f]	0	0%	1	<1%[f]
PRURITUS	1	<1%[f]	0	0%	1	<1%[f]
SKIN DIS	1	<1%[f]	0	0%	1	<1%[f]
SPEECH DIS	1	<1%[f]	0	0%	1	<1%[f]
ASTHMA	0	0%	1	<1%[f]	1	<1%[f]
BRONCHITIS	0	0%	1	<1%[f]	1	<1%[f]
CARCINOMA CERVIX	0	0%	1	<1%[f]	1	<1%[f]
CARDIOMYOPATHY	0	0%	1	<1%[f]	1	<1%[f]
FIBRILLAT ATR	0	0%	1	<1%[f]	1	<1%[f]
HEART FAIL RIGHT	0	0%	1	<1%[f]	1	<1%[f]
HEM GI	0	0%	1	<1%[f]	1	<1%[f]
INFECT	0	0%	2	<1%[f]	2	<1%[f]
NERVOUSNESS	0	0%	1	<1%[f]	1	<1%[f]
SINUSITIS	0	0%	1	<1%[f]	1	<1%[f]

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.
[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).
[c] Number of subjects evaluable for safety.
[d] Number of subjects who reported adverse events within specified Treatment Group and Body System.
[e] Percent of subjects who reported adverse events within specified Treatment Group and Body System: (n/N)*100.
[f] Percentage <0.5% are reported as <1%.

See Appendix Table 2 for more details.
Source TJ4346: /home3/tj4346/iss/s-asopgm/tab22b.sas 10-Sep-99

Table 9 is a summary of subjects in all studies who discontinued tablets due to adverse events during active treatment or placebo follow-up phases. A total of 59 subjects, 41 on Ome-Mg and 18 on placebo discontinued study participation due to an AE. The most commonly reported AEs experienced by Ome-Mg treated subjects were headache (10 subjects), nausea (10 subjects) and vomiting (8 subjects). These were distinct from the most commonly reported AEs for placebo treated subjects which were diarrhea (5 subjects), abdominal pain (4 subjects) and nausea (3 subjects). Of the 41 Ome-Mg treated subjects 28 were treated with 20 mg doses and 13 were treated with 10 mg doses. Of the 28 cases in the 20 mg dose group, in 16 cases the medication was considered 'possibly causative' and in 5 cases 'probably causative'. Causes for discontinuation of Ome-Mg also included rash (3 cases), fever (2 cases), and 1 death. The only fatality

which occurred during all of the OTC studies is not ascribable to Ome-Mg since it occurred in an individual with polydrug intoxication who had stopped taking the study medication 10 days earlier. Overlapping with these cases of drug discontinuation were 24 cases of SAEs in individuals who received Ome-Mg in the OTC studies. In one case the study subject who had received Ome-Mg 10 mg doses developed serum sickness which was considered 'probably related' to administration of the test drug. In a comprehensive composite of all AEs for the 8,179 subjects who were administered Ome-Mg and the 3,120 subjects who were administered placebo 11 cases of liver function abnormalities (6 cases of SGOT elevation, 7 cases of SGPT elevation), 4 cases of urticaria, 3 cases of eye disorders and 1 case of vision abnormality occurred (see Appendix 1, Table 1).

Prescription formulation of Omeprazole - Clinical Trial Adverse Events

To gain a full appreciation of the range of side-effects that are associated with the administration of omeprazole the sponsor has presented a review of AEs observed in all clinical trials that have been performed previously to study the prescription formulation of omeprazole in the treatment of GERD, erosive esophagitis and dyspepsia. Patient populations that have been excluded from this composite analysis include those with peptic ulcer disease and severe hypersecretory conditions (eg Zollinger-Ellison Syndrome). In the analysis 6 US trials conducted by Astra Merck and Merck & Co. Inc. and 29 non-US clinical trials conducted by Astra Hassle were evaluated. The analysis encompassed over 7,500 patients including a total of 5,757 unique patients who were exposed to omeprazole (see Table 2, Appendix).

Despite the fact that the trials were characterized by a number of different study designs the sponsor has presented an overall safety profile of omeprazole for daily doses ranging from 10 mgs to 40 mgs, with duration of exposure from 1 day to 12 weeks in the 'short-term' trials and from above 12 weeks to 1 year for 'long-term' trials (long-term drug exposure for periods longer than 1 year has been presented separately by the sponsor and will be discussed below). For the purpose of analysis the trials have been grouped as shown in Figure 4.

Group	Geography	Duration	Trial Type	No. of Trials
1*	Non-US	≤12 weeks	Well Controlled/Comparative	14
2**	US	≤12 weeks	Well Controlled/Comparative	4
3	Non-US	≤12 weeks	Controlled and Uncontrolled	19
4	US	≤12 weeks	Controlled and Uncontrolled	5
5	Non-US	>12 weeks	Well Controlled/Comparative	5
6	US	>12 weeks	Well Controlled/Comparative	1
7***	Non-US	>12 weeks	Controlled and Uncontrolled (Open-label or Weekend or On Demand)	6

* Group 1 is a subset of Group 3
** Group 2 is a subset of Group 4
*** Group 7 is a unique grouping of long term Non-US studies with no US comparison group

Fig. 4 - Characteristics of Seven Safety Groupings

Although these groupings are useful for the purpose of distinguishing AEs associated with the US vs the non-US study subjects as well as differences in short and long-term treatment, a major limitation of the analysis flows from the fact that only 1,086 unique omeprazole-treated patients are represented in both the US short and long-term trials and only 4,671 unique omeprazole-treated patients are represented in the non-US trials. Therefore, rare and very rare AEs including SAEs that have been linked to omeprazole may not be detected in this analysis. For example, in the case of the US studies, a predicted event rate less than 1 per 333 unique patients would not inevitably occur in the population size that has been analyzed. Likewise, the non-US population and event rate less than 1 per 1,200 unique patients exposed to omeprazole would not necessarily be detected. Therefore, it needs to be emphasized that compilation of a comprehensive list of rare SAEs associated with omeprazole mostly is derived from the post-marketing voluntary reporting system of the prescription formulations (SafeTNet) that has been provided. This will be discussed below. A second limitation of an analysis of the AEs linked to the clinical trials is the diminishing numbers of patients exposed to omeprazole over increasing durations of treatment (see Figures 5, 6 and 7).

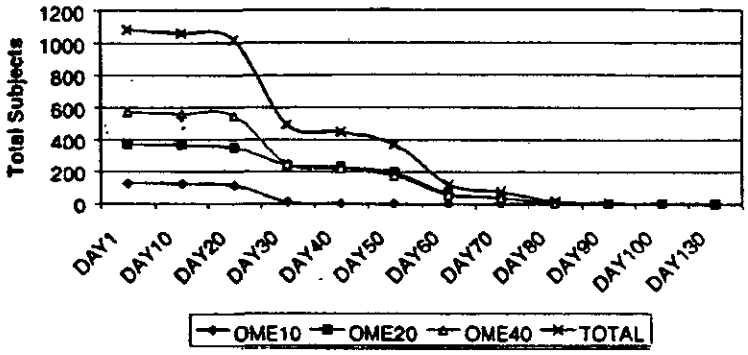

Fig. 5 - Duration of Treatment with OME and by Dose in US Short-Term Studies

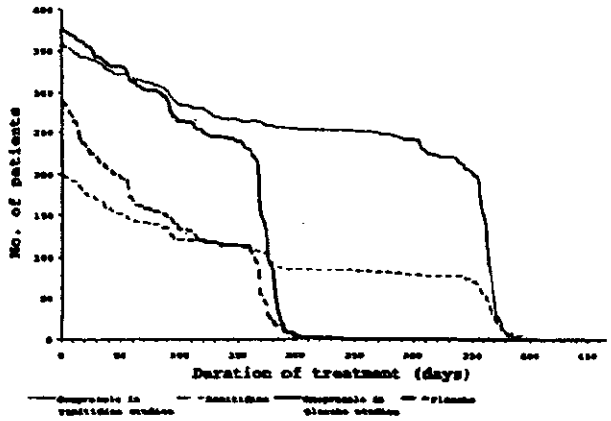

Fig. 6 - Duration of Treatment in Non-US Long Term GERD and EE Comparative Trials

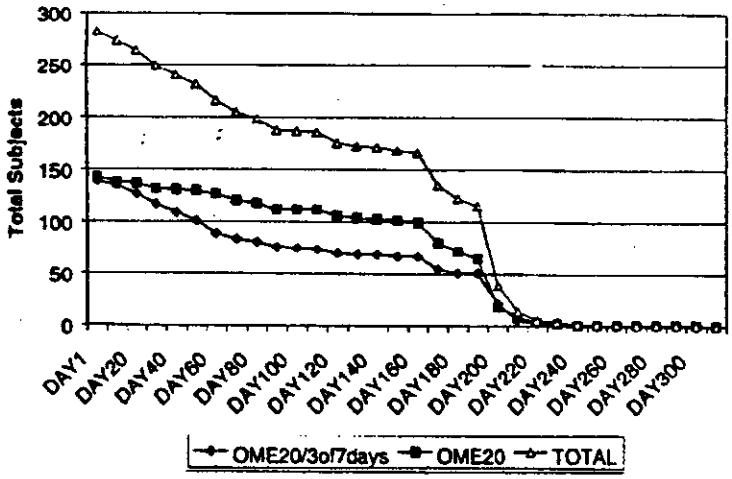

Fig. 7 - Duration of Treatment With OME and by Dose in US Long Term Studies

In the case of US short-term studies, beyond 20 days of treatment, patient numbers diminished rapidly. In the case of US long-term studies, the group exposed to omeprazole for more than 180 days was characterized by dramatically diminishing patient numbers.

A third limitation in the analysis of AEs associated with the clinical studies is the negligible representation of certain demographic groups. This phenomenon is demonstrated in Table 10 which depicts the demographic characteristics of US subjects in short-term well-controlled and/or comparative studies. By age, representation of adolescents (12-17 years) was absent. In addition, with regards to race representation of Asians was negligible. As discussed above, because of the potential for different susceptibilities to side-effects based on differences in CYP2C19 activity, full elucidation of the safety profile of omeprazole in Asians and others with a significantly higher incidence of genetic polymorphisms is an important goal in the completion of a comprehensive analysis. Similar deficiencies in demographic representation were observed in the composite of long-term studies performed in the US (see Table 11).

TABLE 11
Ome Rx Demographic Data by Indication
US Erosive Esophagitis Patients
Long Term (>12 weeks) Controlled Trials[a]
Group 6

	Ome Rx[b] (N =275)[c]		Placebo (N =131)[c]	
	n[d]	%[e]	n[d]	%[e]
Gender				
Female	77	28.0	34	26.0
Male	198	72.0	97	74.0
Unknown	0	0	0	0
Overall	275	100	131	100
Age (Years)				
12 - 17	0	0	0	0
18 - 64	217	78.9	99	75.6
≥ 65	58	21.1	32	24.4
Unknown	0	0	0	0
Overall	275	100	131	100
Range:	18 - 80		22 - 83	
Mean:	51.4 ± 14.1		53.9 ± 14.5	
Median:	52		58	
Race				
Asian	0	0	0	0
Black	13	4.7	8	6.1
Caucasian	253	92.0	119	90.8
Multi/Other	9	3.3	4	3.1
Unknown	0	0	0	0
Overall	275	100	131	100

[a] Trial Merck #010.
[b] Omeprazole treatment includes 20 mg.
[c] Number of patients randomized to each treatment group.
[d] Number of patients within specified parameter, treatment group, and category.
[e] Percent of patients within specified parameter, treatment group, and category: (n/N)*100.

The sponsor has provided little information concerning the breakdown of study subject age groups and minority representation to determine if adequate representation of adolescents and diverse racial groups were achieved in the non-US studies. The sponsor has compiled a list of the most common AEs. In various groupings of the clinical study populations the most common events in these listings did not substantially depart from those published in the Physician Desk Reference which was based on a US clinical trial population of 465 patients who were treated for duodenal ulcers, Zollinger-Ellison Syndrome and resistant ulcer patients. In conjunction with headache, diarrhea, nausea and vomiting, and respiratory infection in some studies elevations of liver transamineses were noted in a small percentage of patients (see Appendix, Table 5). Upon examination of demographic groupings no substantial differences were observed between various races or groups including geriatric individuals vs younger subjects. With regards to gender, differences in adverse event reporting were observed in the US short-term controlled and uncontrolled trials. These include omeprazole-linked monoliasis in 0.8% in female study subjects treated with omeprazole vs 0% treated with placebo and gastroenteritis in 1% of females treated with omeprazole vs 0% treated with placebo.

These side-effects were absent/negligible in males. Conversely, elevation of transaminases including SGOT and SGPT were more frequent in omeprazole-treated males compared to females (2.05 vs 0.5%). With the exception of monoliasis it is not possible to distinguish whether the rates of these adverse events are meaningfully different from background rates of placebo users or between genders, due to the small numbers of study subjects.

Table 6 in the Appendix demonstrates AEs associated with different daily doses of omeprazole (10 mg, 20 mg and 40 mg). Although there are small differences in the rates of headache, diarrhea and nausea these do not appear to be meaningful. Interestingly, rates of elevation of transaminases do not appear to have been affected by the daily doses of omeprazole (10-40 mg range). In the short-term controlled and uncontrolled US clinical trials the most common AEs which led to discontinuation of omeprazole usage were diarrhea, nausea and vomiting. Rates of discontinuation in these categories were no different than discontinuation rates in those treated with placebo (see Appendix, Table 7). It should be pointed out that in these studies, elevation of liver transaminases, episodes of acute gastroenteritis and of visual blurring were each responsible for the cessation of omeprazole in single individuals. The association of these side-effects with omeprazole will be discussed below. In the non-US long-term trials, angioedema and rash were both causes of cessation of omeprazole in single individuals (see Appendix, Table 8.

SAEs/Fatalities Associated With Clinical Trials of the Prescription Formulation of Omeprazole

In the non-US trials fatalities which occurred do not appear to be related to the study drug. In the short-term controlled and uncontrolled non-US trials there were 3 nonfatal SAEs which appeared to be related to the drug. These included drug-associated arthralgia/enterocolitis, bronchospasm, and interstitial nephritis (see Appendix, Table 9). Importantly, common side-effects associated with omeprazole such as nausea, vomiting and diarrhea were occasionally listed as SAEs, inferring that in some cases such symptoms caused significant morbidity in study patients. This is demonstrated in US short-term controlled and uncontrolled trial tabulations in which nausea and vomiting each accounted for a 0.5% rate of SAEs (see Appendix, Table 10). In addition, SAEs marked by body ache, chest pain and fever were recorded as SAEs in 2 patients each. In the placebo arm of these studies the rate of SAEs was negligible, supporting an association of the aforementioned symptoms (when described as SAEs) and omeprazole. Other drug-related SAEs in the US short-term studies included pancytopenia (1 case), pancreatitis (1 case), thrombocytopenia (1 case), bacterial infection (1 case) and acute gastroenteritis (1 case). Consistent with these findings, in the non-US long-term controlled and uncontrolled trials the administration of omeprazole was linked to 2 cases of pancreatitis, 1 case of angioedema and 1 case of gastroenteritis. In contrast, SAEs in the placebo arm of these sutdies were negligible. Despite the fact that SAEs were mostly recorded in the active treatment group who were administered omeprazole and not in those administered placebo the total number of patients in each group were discrepant, as there were more subjects who were treated with the PPI. Because of this difference in

numbers of study subjects it is possible that some of the SAEs linked to omeprazole in these studies are manifestations of background rather than drug-related events.

Based on the data from the clinical trials previously conducted on the prescription formulation of omeprazole in the disease states of GERD and Dyspepsia that have been described above, the sponsor has made the following conclusions:

- In general, the short-term trials demonstrate that diarrhea and headaches are the most frequently recorded AEs associated both with the omeprazole and the placebo groups.
- For trials less than 12 weeks in duration, omeprazole has a safety profile which is similar to placebo.
- Based on the long-term clinical trials, the adverse event profiles were similar for omeprazole and placebo.
- There were no meaningful differences in the adverse event profiles for omeprazole when evaluations were performed according to age, race, gender, dose or duration of use.
- The rate of discontinuation from the clinical trials due to AEs were lower in the omeprazole groups than the placebo groups.
- Fatalities that occurred in the clinical trials were unlikely to be due to trial medication.
- SAEs that were reported in the clinical trials were not considered to be related to omeprazole, in most instances.
- Based on the data presented, it is suggested that omeprazole is safe for OTC use.

Because of the limitations in study design and patient numbers that this reviewer has enumerated above definitive conclusions concerning the linkage between omeprazole and rare or very rare adverse events cannot be drawn. In fact, postmarketing experience with omeprazole has demonstrated that certain uncommon AEs that were detected in the clinical trials are indeed linked to treatment with omeprazole AEs, such as liver toxicity, pancreatitis, agranulocytosis, toxic epidermal toxic epidermal necrolysis can present with a spectrum of severity. In some instances, these AEs have led to death. The specific side-effects will be more extemsively discussed below. It is noteworthy that even common side effects of the drugs such as headache, diarrhea, nausea and vomiting have occasionally been listed as SAEs by patients and/or their physicians, inferring that occasionally they may be associated with significant morbidity. Finally, certain demographics subsets including adolescents 12 years of afe or older and Asian individuals have not been adequately studied to determine whether they manifest differential vuerabilities to toxicity by omeprazole.

Prescription Formulation of Omeprazole - Postmarketing Surveillance Data

The sponsor Astra-Zenica LP maintains a database of drug experience reports related to the patient usage of omeprazole which is called SafeTNet. This database contains both domestic and foreign serious post-marketing AEs and domestic non-serious post-marketing AEs. In addition, SafeTNet contains the SAEs from clinical trials world-wide. In the database, adverse events in a single individual which are associated medically and/or temporally are grouped together in a single case which can be identified by a unique product safety and epidemiology (PSE) ID number. In the submission, the SafeTNet database was searched for reports accumulated and verified on or before June 30, 1998 that were linked to oral omeprazole as the suspected medication causing the side effects. A total of 7,344 cases that encompassed 15,385 adverse events were retrieved. The database, which has been generated through the voluntary reporting of physicians, healthcare professionals and patients reflects widespread usage of omeprazole in 103 countries for various acid-related gastrointestinal disorders. The sponsor has estimated that approximately ——— courses of omeprazole patient treatments world-wide encompassing approximately ——— in the US comprise this database. Each single patient treatment is defined as the number of capsules in an average prescription. In Figure 8, the number of courses of patient treatments world-wide calculated on an annual basis is shown.

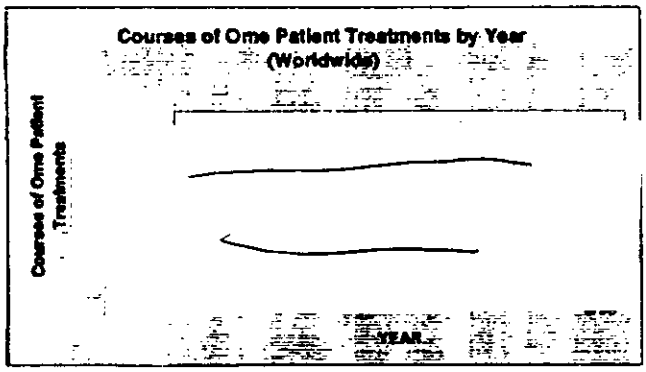

Fig. 8 -

Figure 9 displays the number of reported SAEs world-wide on an annual basis. Although varying from year to year, the numbers of these events year to year have not followed a trend of substantial change. As in the case of the clinical trials discussed above, the most commonly reported adverse events were diarrhea, headache, nausea, abdominal pain and rash. In the database there were a total of 287 deaths, 142 of which were coded as an adverse event. The database also contains 108 cases of urticaria, 97 cases of hepatitis, 74 cases of hepatic function abnormality, 72 cases of leukopenia, 74 cases of interestitial nephritis, 67 cases of pancreatitis, 67 cases of vision abnormalities and 65 cases of pancytopenia. Each os these side effects will be discussed below in a section devoted to topics of concern related to the safety profile of omeprazole. It should be emphasiced

that the absolute number of patient counts that have been tabulated cannot be extrapolated to the true incidence in the US of omeprazole users. This limitation flows from the voluntary nature of the reporting system and the absence of a comprehensive system of detecting and reporting side effects in the omeprazole-treated population. Thus, the main value of these reports is that they form a basis to identify "signals" of side effects that are linked to omeprazole.

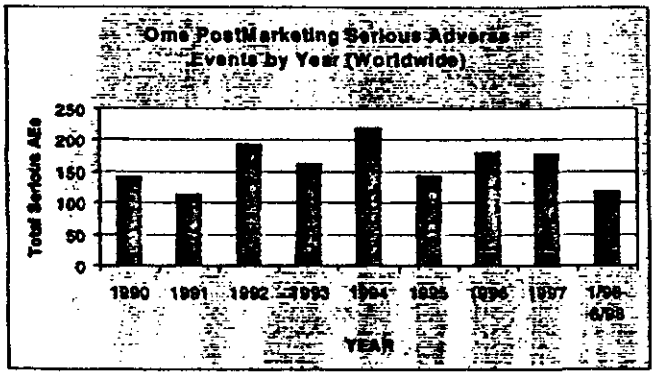

Fig. 9 -

Table 12 demonstrates the world-wide serious post-marketing reports of fatal adverse events in descending frequency for the top 50 terms.

TABLE 12
Worldwide Serious Post-Marketing Reports
Fatal Adverse Events
Descending Frequency for Top 50 Terms
AstraZeneca LP SafeTNet Database
(Page 1 of 2)

Adverse Event	Patient Count
DEATH	142
MYOCARDIAL INFARCTION	20
SEPSIS	18
CARDIAC ARREST	16
HEPATIC FAILURE	15
CARDIAC FAILURE	13
PNEUMONIA	12
THROMBOCYTOPENIA	12
RESPIRATORY INSUFFICIENCY	11
AGRANULOCYTOSIS	9
DEATH FOETAL	8
GI HAEMORRHAGE	8
CARCINOMA	7
PANCYTOPENIA	7
ABORTION	6
CEREBROVASCULAR DISORDER	6
GASTRIC CARCINOMA	6
CIRCULATORY FAILURE	6
RENAL FAILURE ACUTE	5
URAEMIA	5
ARRHYTHMIA	5
NEOPLASM NOS	4
INFECTION	4
MARROW DEPRESSION	4
ANAEMIA APLASTIC	4
CORONARY ARTERY DISORDER	4
LEUKOPENIA	4
HEPATIC FUNCTION ABNORMAL	4
PANCREATITIS	4
PULMONARY INFARCTION	4
CONGESTIVE HEART FAILURE	3

Patient Count = Number of patients who reported the specified adverse event

TABLE 12 (continued)
Worldwide Serious Post-Marketing Reports
Fatal Adverse Events
Descending Frequency for Top 50 Terms
AstraZeneca LP SafeTNet Database
(Page 2 of 2)

ADVERSE EVENT	PATIENT COUNT
GRANULOCYTOPENIA	3
HYPONATRAEMIA	3
HEPATIC NECROSIS	3
MULTIORGAN FAILURE	3
INTERACTION	3
DISSEM. INTRAVASC. COAG.	3
SUDDEN DEATH	3
SEPTIC SHOCK	3
EPIDERMAL NECROLYSIS	3
CEREBRAL HAEMORRHAGE	3
GI NEOPLASM MALIGNANT	2
LYMPHOMA MALIGNANT	2
SEPTICAEMIA	2
PERITONITIS	2
ABDOMINAL PAIN	2
COMA	2
ANENCEPHALY	2
JAUNDICE	2
COLITIS PSEUDOMEMBRANOUS	2

Patient Count = Number of patients who reported the specified adverse event

The fatalities associated with hepatic failure agranolocytosis, pancytopenia, marrow depression, leukopenia, hepatic function abnormalities, pancreatitis, hepatic necrosis, and epidermal necrolysis underline the important point that although these omeprazole linked SAEs are uncommon they can lead to death. This must be taken into account in the formulation of a risk/benefit equation for the OTC use of omeprazole. The association of the fatal SAEs listed above with omeprazole is reinforced in the tabulation of world-wide serious post-marketing reports of non-fatal adverse events in descending frequency for the top 50 terms are shown (see Table 13).

TABLE 13
Worldwide Serious Post-Marketing Reports
Non-Fatal Adverse Events
Descending Frequency For Top 50 Terms
AstraZeneca LP SafeTNet Database
(Page 1 of 2)

Adverse Event	Patient Count
THROMBOCYTOPENIA	96
HEPATITIS	63
NEPHRITIS INTERSTITIAL	57
FEVER	53
INTERACTION	50
CONFUSION	49
VOMITING	44
PANCYTOPENIA	43
HYPONATRAEMIA	42
PANCREATITIS	42
NAUSEA	39
LEUKOPENIA	38
ABDOMINAL PAIN	38
HEPATIC FUNCTION ABNORMAL	36
JAUNDICE	35
RENAL FAILURE ACUTE	30
AGRANULOCYTOSIS	29
CHEST PAIN	29
URTICARIA	27
ANAEMIA HAEMOLYTIC	27
DIARRHOEA	26
HEADACHE	25
ANAEMIA	24
DYSPNOEA	23
URAEMIA	23
GI HAEMORRHAGE	22
CARCINOMA	22
ANGIOEDEMA	22
RASH	22
DIZZINESS	21
ASTHENIA	21
HALLUCINATION	21
HEPATITIS CHOLESTATIC	20
NEUTROPENIA	20
NEUROSIS	18
MYALGIA	18
COMA	17
PRURITUS	17
CONVULSIONS	17
STEVENS JOHNSON SYNDROME	17
NEOPLASM NOS	17
SYNCOPE	17
OVERDOSE	16
GASTRIC CARCINOMA	16
ENCEPHALOPATHY	16
PNEUMONIA	16
AGITATION	16
ARTHRALGIA	16
SEPSIS	15
EPIDERMAL NECROLYSIS	15

Patient Count = Number of patients who reported the specified adverse event

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The sponsor has requested approval for omeprazole OTC marketing in patients 12 years of age and older. a profile of the 190 worldwide serious and US non-serious adverse events in adolescents has been performed for individuals age 12 to 16 years. This safety analysis is severely limited by the relatively small number of adolescent subjects entered into the database. Most likely, the paucity of data reflects both less usage and possibly a reduced reporting rate in this age group, compared to adult individuals. That the repertoire of side effects in this age group is qualitatively and/or quantitatively different than in adult patients is unlikely. However, significant age related side effects cannot be ruled out.

Significant differences in commonly reported AEs in individuals 65 years or older, compared to younger adults, were not noted. Table 14 lists the individual adverse events in decreasing order of frequency with the top 50 adverse events experienced by the 2,050 patients represented in the database age 65 years or older. In this table, the most commonly reported adverse events are diarrhea, nausea, rash, headache and dizziness, mirroring the repertoire of common side effects observed in younger adults.

TABLE 14
Worldwide Serious and US Non Serious Post-Marketing Reports
Adverse Events for Ages ≥ 65 Years
Descending Frequency for Top 50 Terms
AstraZeneca LP SafeTNet Database
(Page 1 of 2)

Adverse Event	Patient Count
DIARRHOEA	112
NAUSEA	110
RASH	104
HEADACHE	82
DIZZINESS	80
ABDOMINAL PAIN	76
THROMBOCYTOPENIA	68
DEATH	65
CONSTIPATION	54
NEPHRITIS INTERSTITIAL	53
PRURITUS	48
CONFUSION	48
EFFICACY, LACK OF	47
FEVER	44
MOUTH DRY	43
PANCYTOPENIA	39
VOMITING	38
ASTHENIA	36
HYPONATRAEMIA	35
CHEST PAIN	31
MALAISE	31
BACK PAIN	31
FATIGUE	31
LEUKOPENIA	31
ALOPECIA	30
ANAEMIA	30
FLATULENCE	29
OEDEMA	29
URTICARIA	28
Adverse Event	**Patient Count**
COUGHING	26
INSOMNIA	26
PAIN	26
RENAL FAILURE ACUTE	25
NEUROSIS	24
HEPATIC FUNCTION ABNORMAL	24
AGRANULOCYTOSIS	23
PARAESTHESIA	23
THERAPEUTIC RESPONSE DECREASED	23
TASTE PERVERSION	22
MYALGIA	22
BLOATING	22
INTERACTION	22
PNEUMONIA	21
WEIGHT DECREASE	20
DYSPNOEA	20
ARTHRALGIA	20
ANAEMIA HAEMOLYTIC	19
BODY AS A WHOLE - GENERAL DIS NOS	19
DEPRESSION	19
HALLUCINATION	19

Patient Count = Number of patients who reported the specified adverse event

Table 11 in the Appendix demonstrates a tally of the worldwide serious and US non-serious post-marketing reports adverse event counts by body system and adverse event term. This is a comprehensive listing both by patient counts and AE term count of adverse events associated with the use of omeprazole in the post-marketing experience. Analysis of this table is limited by the contamination with unrelated medical conditions. Nonetheless, included in this comprehensive list are events that are not coincidental with omeprazole administration. These will be discussed topically in a series of separate sections below.

Special Topics of Safety (including rare adverse events) That Are Related to the Short-term Use of Omeprazole

The following adverse effects have been observed in individuals, even after short-term use of omeprazole.

- hepatic dysfunction
- cardiac function
- acute pancreatitis
- toxic epidermal necrolysis (TEN)
- Angioedema/anaphylaxis
- Visual disturbances
- Drug-drug interactions

An analysis of post-marketing reports, clinical trial data and a review of worldwide literature has been provided. In addition, safety issues in special patient populations and alterations of metabolism and dosage requirements have been discussed. Special populations addressed are:

- Subjects with hepatic impairment
- Subjects with renal impairment
- Geriatric subjects
- Pediatric subjects
- 'Slow' omeprazole metabolizers
- Pregnant subjects

Omeprazole Related Liver Injury

The spectrum of liver toxicity associated with omeprazole treatment ranges from asymptomatic transient elevations of liver enzymes to occasional cases of fulminate hepatic failure. Mild increases of serum transaminases of approximately twice the upper limit of normal occur in less than 1% of patients and apparently do not increase with long term use. In most cases, ALT levels tend to return to normal during treatment with the drug. However, rare cases of severe liver toxicity have occurred as a result of omeprazole treatment.

In non-clinical toxicology studies omeprazole has demonstrated a low potential for hepatotoxicity. In a clinical setting, drug induced liver abnormalities can be divided into a number of categories. These are reflected by the pattern of perturbations of liver function tests, the presence or absence of hepatocellular necrosis, the mechanism of toxicity (eg, immunologically mediated hypersensitivity responses, metabolic toxicity, etc.), the rate of onset and the severity of necrosis and the presence or absence of fibrosis. Typically, liver functions test abnormalities indicate one of the following groups of pathological perturbations which can often be confirmed by liver biopsy.

- Hepatocellular toxicity (elevated serum transaminases)
- Cholestasis (elevated alkaline phosphatase and/or total bilirubin; minimal elevation of transaminases)
- Hepatocellular necrosis (significant elevation of serum transaminases greater than 3 times the upper limit of normal)
- Mixed hepatocellular cholestatic injury (elevation of both transaminases and alkaline phosphatase/total bilirubin).

The sponsor presented data obtained from 4 US (853 patients) and 5 non-US (556 patients) clinical omeprazole trials. The duration of treatment ranged from 4 weeks to 15 months. After initial screening, the advent of elevated liver function tests did not appear to be dependent on dosage regimens. Therefore, AEs in subjects treated with omeprazole 20 mg and 40 mg doses were combined. Toxic events were scored only once on a per patient basis with the highest laboratory value and the peak levels of elevated liver function tests being recorded. The clinical trials that were analyzed in this fashion are listed in Table 15.

TABLE 15
Clinical Trials Used in the Evaluation of Liver Function Tests

Trial No./ Location	Trial Design / Laboratory Draws	Trial Duration and Omeprazole (Ome) Therapy	Total # of Patients on Ome Therapy	Gender
Astra Trial I-603 Multicenter Belgium	TRIAL DESIGN: A double-blind, randomized, parallel trial in patients with reflux esophagitis. Those patients randomized to omeprazole dosed for 4 weeks (up to 8 weeks if healing did not occur). LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn at baseline, week 4, and week 8 (if applicable)	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: Omeprazole 40 mg od	23 8	Male Female
Astra Trial I-609A Multicenter Australia	TRIAL DESIGN: A double-blind, randomized trial in patients with erosive peptic esophagitis. Those patients randomized to omeprazole dosed for 4 weeks (up to 8 weeks if healing did not occur). LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn at baseline, week 4, and week 8 (if applicable)	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: Omeprazole 20 mg od Omeprazole 40 mg od	24 8	Male Female
Astra Trial I-609B Multicenter Australia	TRIAL DESIGN: A double-blind, randomized, parallel trial in patients with erosive/ ulcerative esophagitis. Subjects dosed with omeprazole for 4 weeks (up to 8 weeks if healing did not occur). LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn at baseline, week 4, and week 8 (if applicable)	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: Omeprazole 20 mg od Omeprazole 40 mg od	92 82	Male Female
Astra Trial I-619 Multicenter Belgium, France	TRIAL DESIGN: A double-blind, randomized, parallel trial in patients with erosive/ ulcerative esophagitis. Those patients randomized to omeprazole dosed for 4 weeks (up to 8 weeks if healing did not occur). LABS: Alkaline phosphatase, total bilirubin, and SGPT were drawn at baseline, week 4, and week 8 (if applicable)	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: Omeprazole 20 mg od	55 20	Male Female

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TABLE 15 (continued)

Clinical Trials Used in the Evaluation of Liver Function Tests

Trial No./ Location	Trial Design / Laboratory Draws	Trial Duration and Omeprazole (OME) Therapy	Total # of Patients on OME Therapy	Gender
Astra Trial 0-641 Multicenter Scandinavia	TRIAL DESIGN: Trial consisted of two parts: an initial healing phase and a maintenance phase, in patients with erosive/ulcerative esophagitis. The first part, during the first 3 days, was double-blind and randomized with parallel omeprazole 20 mg and 40 mg groups, followed by open omeprazole treatment. The second part was a double-blind, randomized trial with three parallel groups (two being omeprazole 10 mg and 20 mg). Subjects who relapsed from the maintenance phase continued on with omeprazole 20 mg open maintenance treatment. LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn at baseline, week 6, week 12 (if applicable), and 12 months (or 3, 6, or 9 months, where applicable)	TRIAL DURATION: 15 months total Daily dose day 1-3: Omeprazole 20 mg od Omeprazole 40 mg od Open daily dose day 4-12 weeks: Omeprazole 20/40 mg od Followed by an additional 12 months maintenance period with daily dose: Omeprazole 10 mg od Omeprazole 20 mg od Patients who relapsed from the maintenance phase entered open maintenance treatment for the remainder of the maintenance period with daily dose: Omeprazole 20 mg od	176 88	Male Female
Astra Merck Trial #037 Multicenter US	TRIAL DESIGN: A double-blind, randomized, parallel trial in patients with moderate to severe heartburn associated with GERD. Those patients randomized to omeprazole dosed for 4 weeks. LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn on day 1 and day 28	TRIAL DURATION: 4 weeks Daily dose week 1-4: Omeprazole 10 mg od Omeprazole 20 mg od	126 110	Male Female
Astra Merck Trial #100 Multicenter US	TRIAL DESIGN: A two phase, prospective, double-blind, randomized trial in patients with GERD who did not respond to a 6-week, open-label treatment of ranitidine 150 mg twice daily (Phase 1). Subjects randomized to omeprazole in Phase 2 dosed for 8 weeks. LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn on days 1, 42, and 98	TRIAL DURATION: Phase 1 = 6 weeks Phase 2 = 8 weeks Phase 1: open-label Daily dose Ranitidine 150 mg bid Phase 2: Daily dose week 1-8 (double-blind, randomized treatment) Omeprazole 20 mg od	65 91	Male Female
Merck Trial #005 Multicenter US	TRIAL DESIGN: A double-blind dose ranging trial to evaluate omeprazole in healing and symptomatic relief in patients with moderate to severe erosive esophagitis. Those patients randomized to omeprazole dosed for 4 weeks (up to 8 weeks if healing did not occur). LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn on day -3, week 2, week 4, and week 8 (if applicable)	TRIAL DURATION: 4-8 weeks Omeprazole 20 mg od Omeprazole 40 mg od	131 53	Male Female
Merck Trial #010 Multicenter US	TRIAL DESIGN: A multi-center, double-blind, randomized trial evaluating the effects of omeprazole 20 mg (once daily or 3 out of 7 days) during 6 months of continued treatment of patients with erosive esophagitis who were healed following 4-8 weeks of omeprazole 40 mg treatment. LABS: Alkaline phosphatase, total bilirubin, SGOT, and SGPT were drawn on day 1, week 12, and week 24 (or at final visit)	TRIAL DURATION: 28 – 32 weeks Phase 1: open-label healing phase Daily dose omeprazole 40 mg od Phase 2: maintenance phase Omeprazole 20 mg od Omeprazole 20 mg 3 of 7 days	200 77	Male Female

A depiction of the liver function abnormality groupings in the non-US and US trials is summarized in Tables 16 and 17, respectively. Of 556 patients in the non-US trials, 9 manifested a hepatocellular toxicity pattern; 1 developed elevated transaminases over a 3-fold increase above the upper limit of normal consistent with a significant hepatocellular necrosis. In addition, 31 patients developed a cholestatic picture with elevated alkaline phosphatase; another 14 developed isolated hyperbilirubinemia. Although 177 of the 556 patients in the non-US clinical studies had an abnormal liver function test while on omeprazole treatment, significant hepatocellular necrosis can only be ascribed to 10 patients, or less. Similarly, in the US studies, among 853 omeprazole-treated patients, 253 developed an abnormal liver function test while on treatment. Mildly elevated transminases were noted in 31 patients and 5 patients had transaminase elevations of more than 3 times above the upper limit of normal. Assuming that this cutoff is a marker of significant hepatocellular necrosis, these numbers suggest an incidence of approximately 6 per thousand of omeprazole users that develop this condition. It should be emphasized that a majority of patients who developed abnormalities of liver function tests manifested isolated elevations of alkaline phosphase (35) or bilirubin (17) or isolated elevations of transaminases (SGOT, 10, SGPT, 66). Thus, most of the liver function test abnormalities appear to be mild and there is no consistent pattern of perturbation of liver function. In addition, there is no apparent association of these abnormalities with either the dose or duration of omeprazole therapy. Nonetheless, there appears to be a small percentage of patients who develop more significant hepatocellular necrosis with elevations of transaminases above 3 times the upper limit of normal. The incidence of this phenomenon in these studies ranges between approximately 2 per 1000 and 5 per 1000 patients treated with omeprazole.

To further analyze the hepatotoxic potential of omeprazole, the post-marketing surveillance database (SafeTNet) was analyzed. The events that were analyzed included:

- All non-serious post-marketing adverse events in the US
- All serious post-marketing adverse events worldwide
- All serious clinical trial adverse events reported worldwide

The thorough search of adverse event terms were reviewed in the screen of all serious clinical and post-marketing adverse events. This search revealed 261 serious adverse events consistent with hepatic dysfunction. These events were rated by a sponsor designated physician to assign a probability of causal association with omeprazole treatment. There were 4 rating categories that are listed below:

- Category A: Defined as a well documented case with no other explanation for toxicity.
- Category B: Defined as a well documented case with more than one possible explanation or suggestive contributing factor for toxicity.
- Category C: Defined as a case with evidence of the reported adverse event but insufficient information available to determine causality.
- Category D: Defined as a case with no documented evidence of the reported adverse event.

TABLE 16

Liver Function Abnormality Groupings – Summary
OME Non-US Trials

Trials	Total Patients	Rate Category Ch	ETs	Hep	SE - AlkPhos	SE - Bili	SE - SGOT	SE - SGPT	BD	NF
I-603	31	1	0	0	2	0	2	0	8	0
I-609A	32	0	1	0	1	0	0	2	2	1
I-609B	154	3	1	1	11	1	0	5	16	1
I-619	75	3	0	0	5	1	0	3	12	2
I-641	264	10	7	0	12	12	1	26	24	0
		17	9	1	31	14	3	36	62	4

Ch : Cholestatic pattern (elevated transaminase and alkaline phosphatase and/or bilirubin elevation)
ETs: Hepatocellular pattern (elevated transaminases)
Hep: Hepatitis (transaminases > 3x)
SE - AlkPhose, Bili, SGOT, or SGPT: Single enzyme elevation - alkaline phosphatase, bilirubin, SGOT or SGPT
BD : Decrease from abnormal baseline
NF : No follow-up laboratory values available

TABLE 17

Liver Function Abnormality Groupings – Summary
OME US Trials

Trials	Total Patients	Rate Category Ch	ETs	Hep	SE - AlkPhos	SE - Bili	SE - SGOT	SE - SGPT	BD	NF
005	184	3	5	1	9	4		8	14	2
010	277	5	17	3	18	8	8	16	11	
017	236	5	5	1	5	3	1	24	36	
100	156	2	4		3	2	1	18	11	
		15	31	5	35	17	10	66	72	2

Ch : Cholestatic pattern (elevated transaminase and alkaline phosphatase and/or bilirubin elevation)
ETs: Hepatocellular pattern (elevated transaminases)
Hep: Hepatitis (transaminases > 3x)
SE - AlkPhose, Bili, SGOT, or SGPT: Single enzyme elevation - alkaline phosphatase, bilirubin, SGOT or SGPT
BD : Decrease from abnormal baseline
NF : No follow-up laboratory values available

Using these criteria, the following numbers of fatal and non-fatal cases were identified according to their case rating (see Table 18).

TABLE 18
Hepatic Dysfunction – Ratings of Serious Adverse Event Cases

	Case Rating				
Outcome	A	B	C	D	Total
Fatal	2	19	12	0	33
Non-fatal	4	114	99	10	227
Total	6	133	111	10	260

Of the total 33 fatal cases, 2 were assigned an 'A' rating; in at least one of these cases, the patient was dechallenged successfully with resolution of liver function tests. Upon rechallenge with omeprazole, liver enzymes again rose. In a list of a total of 227 involving hepatic dysfunction as SAEs not associated with death, 4 were assigned an 'A' rating. In at least 2 of the 4 cases, the patients were successfully dechallenged and upon repeat challenge with omeprazole either symptoms and/or the transaminase elevations recurred. In one of these cases, the appearance of omeprazole related jaundice, an elevated alkaline phosphatase was not specifically related to an elevation of transaminases. However, in the other, omeprazole induced elevations of the ALT to over one thousand units per liter. In another 'A' case rated patient, the patient, who was treated with omeprazole and no other medications, developed hepatitis with jaundice and possible hepatic failure. Omeprazole was discontinued and the patient recovered within a month. These cases illustrate the potential that omeprazole has to induce severe hepatocellular necrosis and, rarely, liver failure. From the voluntary reporting system it is not possible to assess the incidence of these events.

A review of the literature by the sponsor demonstrates that in a small series of patients, significant omeprazole related hepatotoxicity is unusual. Based on an investigation of medical records from the General Practitioners Research Database that included 108,981 patients who received an H_2 blocker or omeprazole[4], the sponsor has concluded that the risk of acute injury using cimetidine which was estimated to be approximately 1 per 5,000 patients exposed to the drug is qualitatively similar to the risk to develop acute liver injury associated with the use of omeprazole. The sponsor has concluded that this low risk is compatible with the over-the-counter use of these agents. Nonetheless, it should be pointed out that at the severe end of the spectrum of relatively rare omeprazole induced hepatotoxic events are cases of hepatocellular necrosis associated with liver failure and even death. The incidence of these events appears to be similar to those associated with the use of cimetidine and possibly some other H_2 blockers that have been approved previously for OTC marketing in the United States. In the current labeling of OTC cimetidine, no mention is made of the potential for liver toxicity, how it should be

[4] R.S. Fisher et al. Rebound acid hypersecretion after gastric acid suppressant therapy: A short-lived (<1-week) phenomenon. Gastroenterology 1998; 114(4 Suppl Pt 2):A13.

recognized and acted upon by the consumer. Similarly, in the proposed labeling for OTC omeprazole, the sponsor has not made mention of the potential of liver toxicity by this agent. This reflects a minimalist approach to labeling for rare SAEs that are predicted to occur in an undifferentiated OTC population.

Changes in Cardiac Function Associated With Omeprazole

Non-clinical pharmacodynamic toxicological studies reveal that omeprazole has negligible effects on cardiac conduction. After oral or intraduodenal administration to dogs, specifid effects of the drug on the heart have not been observed. In humans, omeprazole does not affect cardiac performance, heart rate or blood pressure. ECG's from pharmacokinetic studies performed in healthy male volunteers were evaluated in these studies, omeprazole was either administered by oral suspension in doses ranging from 0.5 to 100 mg, or by intravenous infusion ranging between 1 and 20 mg. ECGs were performed at pre-baseline, baseline, peak plasma concentration and post-peak plasma concentration timepoints. ECG tracing evaluation by an independent cardiologist was performed in a blinded fashion. In this study, omeprazole did not induce abnormalities of cardiac repolarization. In a survey of cardiac conduction AEs reported in patients administered omeprazole that encompassed serious clinical and serious post-marketing events worldwide through June 30, 1998, the sponsor identified 148 cases of ventricular, supraventricular, or general conduction irregularities of the heart. These were rated on a scale that was identical with that used for the rating of liver toxicity described above (see above).

TABLE 19
Cardiac – Ratings of Serious Adverse Event Cases

	Case Rating				
Outcome	A	B	C	D	Total
Fatal	0	8	14	3	25
Non-fatal	1	60	55	7	123
Total	1	68	69	10	148

As can be seen in Table 19, of the 148 serious fatal/nonfatal conduction disorders that have been reported worldwide, there is only one case that was assigned an 'A; rating. This case represented an episode of persistent bradycardia that developed after bolus IV infusion of omeprazole in a patient with multiple medical problems who was being simultaneously treated with a number of pharmaceutical agents. The sponsor has provided a literature review to demonstrate that omeprazole does not significantly inhibit CYP3A4, an enzyme which metabolizes cisapride and a number of other drugs that have significant effects on cardiac repolarization. Based on the information that has been provided, the sponsor has concluded that there is no clear association between the use of omeprazole and cardiac function or arrhythmic activity, including effects on supraventricular, ventricular and/or general conduction.

Acute Pancreatitis

About 90% of all cases of acute pancreatitis are related either to ethanol ingestion or gallstone disease. Pancreatitis also occurs as a complication of bone marrow transplantation and is associated with certain hyperlipidemias. In addition, a number of drugs have been causally linked with acute pancreatitis. Classification of drugs based on the certainty of causality of acute pancreatitis has been proposed[5]. The proposed classification includes the following categories:

- Drugs with a definite association based on carefully documented studies. These include l-asparaginase, azathioprine, didanosine, estrogens, furosamide, pentamidine, sulfonamides, tetracycline, thiazides, valproic acid, and vinca alkaloids.
- Drugs with a probable association. These include chlorthalidone, corticosteroids, cyclosporine and rifampicin. Drugs with a possible association. These include acetominophen, cisplatin, indomethacin, methyldopa, nitrofurantoin and procainamide.

In a series of pharmacodynamic non-clinical studies, it has been observed that omeprazole induces a decrease in pancreatic fluid volume flow and bicarbonate secretion. These effects may be secondary to a reduction in gastric acid delivery to the duodenum. No toxic effects of omeprazole have been observed on the pancreas in animal models. In the SafeTNet database, a total of 12 fatal and 69 non-fatal serious adverse event cases were recorded (see Table 20).

TABLE 20

Acute Pancreatitis – Ratings of Serious Adverse Event Cases

Outcome	Case Rating				Total
	A	B	C	D	
Fatal	0	7	5	0	12
Non-fatal	0	41	28	0	69
Total	0	48	33	0	81

None of these cases were rated as "A" category cases (well documented cases with no other explanations identified). Because of their complex nature, it is not possible to ascribe causality of the described episodes of pancreatitis to omeprazole. It has been suggested that omeprazole contributes to the risk of developing acute pancreatitis in certain medical settings. In a study of acute pancreatitis in bone marrow transplant patients, omeprazole was not found to be an independent risk factor. However, when examined as an indicator variable in a univariable analysis, the use of omeprazole approached significance (p=0.12). A recently completed epidemiologic trial evaluated the risk of developing acute pancreatitis upon use of H_2 receptor antagonists or PPIs.

[5] M. Runzi, P. Layer. Drug-associated pancreatitis: facts and fiction. Pancreas 1996; 12(1):100-109.

Data were obtained from a cohort of 337 practitioners in the United Kingdom[6]. Those patients with a history of known risk factors other than drug exposure were excluded. A total of 88 cases of idiopathic acute pancreatitis possibly related to drug exposure were identified (see Table 21).

TABLE 21

Acute Pancreatitis - Incidence Rates Observed in Epidemiologic Trial by Eland et al.[10]

Number of Cases	Drug Used	Incidence Rate/100,000 Person-Years (age- and gender-adjusted)	Relative Risk Among Current Users (95% CI)
6	Ranitidine	5.6	1.4 (0.5-4.5)
5	Cimetidine	9.3	2.4 (0.7-8.0)
3	Omeprazole	7.2	1.3 (0.3-5.4)

Marginal increases in the relative risk to develop acute pancreatitis were noted in patients treated with ranitidine, cimetidine or omeprazole. This risk was greater in the first month of therapy, a dose response relationship was not observed. An interpretation of this comprehensive study is that exposure to omeprazole poses a negligible risk in most individuals to develop acute pancreatitis.

Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS)

Numerous drugs have been associated with the development of TEN and SIS. In over 90% of cases of individuals with these medical conditions, drug exposure can be ascribed as a probable cause. Drugs that have been identified with these conditions include:

- Nonsteroidal anti-inflammatory drugs
- Antibacterial agents
- Anticonvulsant compounds, analgesics in drugs used for the management of gout
- Chlorpromazine, vincristine, etrenidate, flouxetine, and fluvoxamine
- Antisecretory drugs including H_2 receptor antagonists and PPI

Other cases of SIS and TEN include: HIV infection, graft vs host disease, bone marrow transplantation, systemic lupus erythematosis, certain neoplasia, vaccinations, and severe viral infections such as herpes simplex, herpes zoster and measles. In many cases, it is difficult to ascribe causality to a single drug because of the clinical context in which patients receive multiple medications. In addition, time intervals between exposure and dermatologic symptoms is often variable, although most reactions occur between 1 and 3 weeks after initial exposure.

[6] I.A. Eland et al., The risk of acute pancreatitis associated with acid-suppressing drugs. In manuscript.

The SafeTNet database was searched for the reports of significant toxic skin reactions in patients exposed to omeprazole. A total of 49 cases were identified (see Table 22).

TABLE 22
Reports of TEN, SJS, and Associated Serious Dermatologic Reactions AstraZeneca LP SafeTNet Database

ADVERSE EVENT TERM	NO. OF SAE'S FROM FATAL CASES	NO. OF SAE'S FROM NON-FATAL CASES	TOTAL
Toxic epidermal necrolysis/Lyell syndrome/ epidermal necrolysis	9	16	25
Stevens-Johnson syndrome	3	15	18
Bullous eruption/dermatitis bullosis	1	3	4
Pemphigoid reaction	0	3	3
Erythroderma	1	1	2
Skin exfoliation	0	2	2
Erythema multiforme severe	0	1	1
Toxicoderma	0	0	0
TOTAL	**14 SAE's**	**41 SAE's**	**55 SAE's**

SAE = SERIOUS ADVERSE EVENT

Based on the aforementioned rating system defining the likelihood of causality, of the 49 cases, 2 were given an 'A; rating (1 fatal, 1 non-fatal). In the non-fatal case, after successful dechallenge with omeprazole, upon reinitiation of therapy, the patient redeveloped the skin lesions. It appears than TEN and SIS are rare but important clinical complications that can occur as a consequence of omeprazole therapy. The incidence of this complication seems to be comparable to that associated with other classes of drugs.

Agranulocytosis and Other Related White Blood Cell Disorders

Drugs that cause agranulocytosis can be categorized according to the mechanism by which white blood cell suppression occurs. Broad drug classes that cause white blood cell suppression include:

- Cytostatic drugs
- Immunosuppressive drugs

- Drugs which induce agranulocytosis and neutropenia as a consequence of idiosyncratic reactions. Such drugs include antithyroid drugs, eg. Propylthioracil, methimazole, carbimazole, nonsteroidal anti-inflammatory agents, eg. Indomethacin, or phenylbutasone, anti-bacterial agents, eg. Penicilllan, doxicyclin, trimethoprim sulfomethoxazole, anti-convulsants eg. Carbamazapine, phenytoin. Rarely, certain H_2 blockers such as cimetidine and ranitidine have been associated with idiosyncratic white blood cell suppression.

The SafeTNet database was screened for serious adverse events of agranulocytosis and other related white blood cell disorders reported through June 30, 1998 (see Table 23)..

TABLE 23

Serious Adverse Events of Agranulocytosis and Other Related White Blood Cell Disorders Reported to AstraZeneca LP through June 30,1998 (derived from SafeTNet)

Adverse Event Term	# of Adverse Events Reported	# of Unique Patients	# of Deaths
Agranulocytosis	40	40	13
Granulocytopenia	17	17	5
Leukopenia	46	45	8
Neutropenia	20	19	0
White Blood Cell Disorders	1	1	0
Total	**124**	**122**	**26**

Of 122 unique omeprazole-treated patients who developed agranulocytosis, granulocytopenia, or leukopenia, 26 died. Case ratings concerning the likelihood of omeprazole-linked toxicity as described previously were assigned to characterize all of the serious cases. Operational definitions included:

- Agranulocytosis - granulocyte count less than or equal to 0.5 $X10^9$ per liter
- Granulocytopenia - granulocyte count less than 1.5 $X10^9$ per liter
- Leukopenia - granulocyte count less than $3.0X10^9$ per liter
- Thrombocytopenia - platelet count less than $100X10^9$ per liter

Based on these definitions, numeric summaries of these serious fatal and non-fatal cases are shown in Tables 24 and 25, respectively.

Of the 26 fatal cases, 5 were attributable with high certainty to omeprazole exposure and were assigned an 'A' rating. Of the total 96 non-fatal cases, 35 were attributable to omeprazole and were assigned an 'A' rating. Although the true incidence of these side-effects cannot be gleaned from the SafeTNet database because it is predicated on a system of voluntary reporting, it is clear from the clinical trial database which was previously discussed that granulocytopenia and leukopenia occurred at rates of 0.2 % and 0.9% respectively in the US short-term controlled and uncontrolled trials (duration of omeprazole treatment was 12 weeks or less). In the long-term US controlled and uncontrolled trials (duration of omeprazole treatment was 12 weeks or more), the incidence of these side-effects was even higher (granulocytopenia and leukopenia occurred at rates of 0.7% and 1.5% of omeprazole-treated subjects, respectively. This was compared to 0% and 0.8% of placebo-treated subjects, respectively. It can be inferred that mild to moderate suppression of white blood cell numbers in the circulation as a consequence of omeprazole treatment is not exceedingly rare. This effect may be influenced by duration of exposure to the drug. It should be emphasized that an accurate assessment of the incidence of agranulocytosis associated with omeprazole cannot be

made from these data. Nonetheless, it is likely that omeprazole-induced agranulocytosis is a relatively rare event. From the Intensive Medicines Monitoring Program (IMMP) that has been established in New Zealand to comprehensively research side-effects of certain drugs in their early post-marketing period, after approval of the prescription formulation of omeprazole, treated individuals were monitored. In a cohort study of 9,260 patients exposed to the PPI. In this cohort, 17 hematologic events were recorded. Of those that appeared to be causally related to omeprazole treatement, there were 3 cases of neutropenia and 1 aplastic anemia. In a study by the French Ministry of Health[7] a spectrum of hematologic effects related to omeprazole were noted. These included pancytopenia, thrombocytopenia, leukopenia and hemolytic anemia. All cases occurred after a mean period of 15 days following initiation of PPI therapy. The rapid onset of these effects suggested to the investigators that toxicity resulted from an immunologic mechanism. From the above, it is clear that severe leukocyte suppression or agranulocytosis caused by omeprazole is a relatively rare event. The post-marketing databank and literature also support a linkage between the PPI and these side effects. Currently, it is not possible to define accurately the incidence of these events. Based on clinical trial data they may occur as frequently as 1/5,000 omeprazole treated patients.

TABLE 24
Numeric Summary of Serious Fatal Cases

	Number of Cases	Number of Cases Fulfilling Agranulocytosis Criteria	A	B	C	D
Agranulocytosis Fatal Cases	13	8	1*	8*	0	4*
	Number of Cases	Number of Cases Fulfilling Agranulocytosis Criteria	A	B	C	D
Granulocytopenia Fatal Cases	5**	2	3*	1*	1	0
Leukopenia Fatal Cases	8**	2	1*	2	2	3*
Total Number of Agranulocytosis/ Granulocytopenia/ Leukopenia Fatal Cases		Total Number of Cases Fulfilling Agranulocytosis Criteria	Total A	Total B	Total C	Total D
26		12	5	11	3	7

* Includes a case(s) fulfilling agranulocytosis criteria
** No hematologic laboratory values were provided in 2 granulocytopenia and 3 leukopenia cases

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[7] Update on the adverse effects of omeprazole. Prescrire Int 1997; 6(29):78-79.
A. Castot et al. Assessment of side effects with omeprazole reported to regional drug monitoring centers during the first 22 months of marketing. Therapie 1993; 48:469-474.

TABLE 25
Numeric Summary of Serious Non-Fatal Cases

	Number of Cases	Number of Cases Fulfilling Agranulocytosis Criteria	A	B	C	D
Agranulocytosis Non-Fatal Cases	27	16	9*	3*	12*	3*
Granulocytopenia Non-Fatal Cases	12	3	4*	3*	5	0
Leukopenia Non-Fatal Cases	37	2	12*	8	13	4*
Neutropenia Non-Fatal Cases	19	10	9*	2	6*	2*
White Blood Cell Disorders Non-Fatal Case	1	0	1	0	0	0
Total Number of Agranulocytosis/ Granulocytopenia/Leukopenia/ Neutropenia/White Blood Cell Disorder Non-Fatal Cases		Total Number of Cases Fulfilling Agranulocytosis Criteria	Total A	Total B	Total C	Total D
96		31	35	16	36	9

* Includes a case(s) fulfilling agranulocytosis criteria

Anaphylaxis and Angioedema

Anaphylaxis and angioedema are associated with exposure to a number of pharmacological agents. The clinical entities are both manifestations of immediate hypersensitivity reactions which are often mediated by IgE antibodies and can be associated with stridor, circulatory collapse and even death. Agents linked to anaphylaxis and angioedema include non-steroidal anti-inflammatory drugs, muscle relaxants, anaesthetics, narcotics and penicillins. Preclinical testing of in guinea pigs has shown that omeprazole has the potential to cause contact hypersensitivity. In human subjects, occupational exposure to the drug has been associated with a positive lymphocyte transformation test. This finding was not linked with evidence of systemic or passive cutaneous anaphylaxis. Post-marketing surveillance for anaphylaxis/angioedema, including both post-marketing and serious clinical trial AEs identified 134 cases (see Table 26).

TABLE 26
Anaphylaxis and Angioedema - Ratings of Serious Adverse Event Cases

Outcome	Case Rating				Total
	A	B	C	D	
Fatal	0	4	3	0	7
Non-fatal	9	52	42	24	127
Total	9	56	45	24	134

Importantly, 48 of these cases were from clinical trials, suggesting that these events are not exceedingly rare. They included 4 cases of angioedema (2 are assigned 'B' rating and 2 are assigned a 'C' rating by the sponsor), 2 cases of urticuria (both "C") and 1 case of anaphylaxis ("B").

Seven of the SafeTNet 134 cases were fatal, 3 of which were observed in clinical trials. Of the 134 cases, 9 were rated as consistent with a category 'A' classification using the same criteria that have been listed above to designate the probability of causality with omeprazole exposure.

The narratives of these cases point to a number of important features. First, symptoms of swelling, wheezing, urticaria, rash, etc. occurred within a short time after the beginning of omeprazole treatment. Second, the symptoms disappeared after dechallenge and reappeared after rechallenge confirming the linkage between omeprazole and the side-effects. Third, the onset of anaphylaxis/angioedema was idiosyncratic and not predictable prior to drug exposure. Although rare, the fact that few cases of anaphylaxis/angioedema have occurred during clinical trials to study omeprazole including a case of angioedema linked to a patient treated with Ome-Mg suggest that this side effect is not exceedingly rare. A number of publications confirm the observation that omeprazole induces immediate hypersensitivity responses in patients. Nonetheless, the empiric experience that has been reported in the literature suggests that severe angioedema/urticaria linked to omeprazole is quite rare. In the Intensive Medicines Monitoring Program (IMMP) in New Zealand, out of 17,365 patients treated with omeprazole there were 8 confirmed reports of angioedema/urticaria. Based upon this study the AE rate for angioedema/urticaria was estimated to be approximately 0.5 per 1,000 patients. Exposure to H-2 receptor antagonists has also been associated with the advent of immediate hypersensitivity reactions.

It is important to note that in the non-US long-term studies of the prescription formulation there were 3 withdrawals due to urticaria, and 1 due to angioedema and 4 due to rash or dermititis. Therefore it is possible that these side effects are not exceedingly rare.

Visual Disturbances

Based on a preclinical model that links omeprazole with anterior ischemic optic neuropathy and the accumulation of several cases of severe visual disturbances, including blindness, reported in severely ill patients receiving an intravenous formulation of omeprazole, the Bundesgesundheitsamt (BGA), the drug authority of Germany, decided to suspend the registration of the injectable bolus form of omeprazole. In the US post-marketing reports of blurred vision, eye irritation and other opthamologic events have been received. A full analysis of this subject will be performed by Dr. Sheldon Kress, Medical Officer in the DGCDP.

Drug-drug Interactions

There is a potential for drug-drug interactions between the PPI and other agents metabolized by CYP2C19 since it is the major cytochrome P450 isoform which is responsible for oxidation of omeprazole in the liver. Like omeprazole, reduced clearance of diazepam has been observed in 'rapid-metabolizers' of omeprazole (patients who produce significant levels of wild-type CYP2C19 activity. In individuals on long-term oral diazapam therapy at steady state drug plasma levels would be expected to be elevated due to corresponding decreased clearance of the tranquilizer. Other drugs whose metabolism is inhibited by omeprazole include phenytoin, R-warfarin and tolbutamide. The effect of omeprazole on plasma levels of phenytoin has been investigated in four different studies. Omeprazole 40 mgs daily causes a 15%-20% increase in plasma levels of phenytoin in healthy volunteers. In contrast, 20 mg doses in patients continuously treated with phenytoin did not significant changes in plasma levels of the anti-epileptic agent. In contrast to S-warfarin, R-warfarin plasma levels are increased by approximately 10% during co-administration of omeprazole. In most clinical contexts in which other drugs are not being administered the effects of co-administration of omeprazole with warfarin are predicted to be small. Likewise, effects on the sulphonylurea antidiabetic medication tolbutamide by omeprazole 40 mg doses are slight (approximately 10%). Other studies have demonstrated little interaction between omeprazole and clarithromycin, cyclosporine, erythromycin, estradiol, lidocaine, nifedipine and quinidine. These drugs are mainly metabolized by CYP3A4. After administration of 20 mg doses of the PPI in 'slow-metabolizers' who have negligible levels of CYP2C19 activity, plasma omeprazole levels are two-fold higher, compared to 'rapid-metabolizers'. This modest rise does not imply that 'slow-metabolizers' are not especially susceptible to drug-drug interactions, since the saturability of other cytochrome P450 isoforms may be significantly less than that of CYP2C19 in 'rapid-metabolizers' of omeprazole. As alluded to above, approximately 3% of Caucasians and 15% of Asians are 'slow-metabolizers'. The vunerabilities that these individuals have to drug-drug interactions can only be tested empirically. Currently, there is a paucity of information about the implications of CYP2C19 polymorphisms on drug-drug interactions.

A separate mechanism of drug-drug interactions between omeprazole and other agents is related to the effect of changing luminal pH on drug absorption. Both digoxin and

nifedipine absorption are increased when omeprazole is coadministered in daily doses of 20 mg or 40 mg. The differences in absorption are modest and generally not clinically meaningful. However, there are some individuals, particularly those who have renal impairment or are especially susceptible to digoxin toxicity in whom subtle changes in digoxin blood may have an undesirable effect. Other drugs such as ketoconazole or itraconazole are poorly absorbed when the luminal pH of the stomach is elevated. In the case of ketoconazole, a decrease in absorption of 80% has been observed after administration of a 60 mg dose of omeprazole[8]. It is predicted that patients who are being treated for fungal infections with ketoconazole/itraconazole will be vunerable to loss of the therapeutic effect, if omeprazole is co-administered. Appropriated labeling to instruct patients of this effects may be necessary to avoid this problem.

Alterations of Metabolism/Clearance of Omeprazole in Special Patient Populations

The metabolism of omeprazole primarily occurs in hepatocytes. In young healthy subjects the half-life of omeprazole is approximately 0.5 - 1hr. It has been determined that even in the face of significant hepatic cirrhosis the elimination half-life of the drug is less than 3 hours. Because it is predicted that when single daily doses of omeprazole are administered further accumulation of the parent drug during steady state will be negligible and dose adjustment is unnecessary. In a study of 8 patients with varying severity of liver disease the metabolism of 40 mg oral and 20 mg IV doses of omeprazole were studied. As shown in Table 27, liver disease did not reduce the bioavailability of the oral formulation of the drug. However, the area under the plasma concentration vs time curve (AUC) was seven-fold higher and the plasma elimination half-life was approximately 4 times longer in hepatically impaired patients than in healthy subjects (2.8 hrs vs 0.7hrs). Because the typical dosing interval of omeprazole is 24 hours, lengthening of the elimination half-life of omeprazole in patients with hepatic cirrhosis to a duration less than 3 hours does not lead to significant increased accumulation of the drug during steady state conditions. Based on this pharmacokinetic prediction it is unlikely that patients with significant liver disease (eg cirrhosis, hepatitis, portal hypertension, portal vein thrombosis, fatty liver, etc.) would be at increased risk for the development of omeprazole-linked AEs compared to normal individuals. The sponsor has presented a summary table of a compassionate use study designed to evaluate the efficacy/safety of the long-term treatment with omeprazole in patients with peptic ulcer disease or severe ulcerative esophagitis resistant to high doses of ranitidine. In the study 41 patients had significant liver disease. Irrespective of the time interval, 80.5% of the subjects reported 1 or more AEs, a similar percentage that has been reported to occur in normal healthy subjects. Although the sponsor has quoted this finding to support the contention that patients with significant liver disease are not predisposed to develop AEs, more complete information is necessary to determine whether this assertion is correct. In particular, different side-effects may occur by distinct mechanisms, some which may be related to drug dosage/serum levels. A comprehensive comparison of specific side effects is necessary to draw any firm conclusions. Theoretically the presence of significant liver disease may alter the extent of drug-drug interactions that occur between

[8] .W.F. Chin et al. Effects of an acidic beverage (Coca-Cola) on absorption of ketoconazole. Antimicrob Agents Chemother 1995; 39(8):1671-1675.

omeprazole and other drugs or their metabolites which are cleared by the liver. For example, clearance of diazapam is decreased independently by the presence of liver disease and the co-administration of omeprazole. Therefore it is likely that omeprazole will accentuate diazapam-linked effects in patients who are hepatically impaired. The sponsor has not provided information to assess scenarios in which drug-drug interactions occur in hepatically impaired individuals.

TABLE 27
Pharmacokinetic Parameter Values Following Administration of Omeprazole in Different Subpopulations - Adjusted to a 40 mg Oral Dose (for AUC, C_{max} and F) and a 20 mg Intravenous Dose (for $t_{\frac{1}{2}}$ and CL)

PARAMETER	YOUNG HEALTHY (N=18)[11]	ELDERLY HEALTHY (N=14)[11]	RENALLY IMPAIRED (N=12)[7]	HEPATICALLY IMPAIRED (N=8)[1]	"SLOW METABOLIZERS" (N=4)[12]
AUC (umol*h/L)	4.0	8.8	2.4	29	18
C_{max} (umol/L)	3.3	5.7	3.2	8.4	4.8
F	0.56	0.76	0.70	0.98	-
$t_{1/2}$ (h)	0.7	1.0	0.6	2.8	2.1
CL (L/min)	0.59	0.25	0.56	0.07	-

Slow metabolizers = lack CYP2C19 enzyme; AUC = area under the plasma concentration versus time curve; C_{max} = maximum plasma concentration, F = absolute bioavailability; $t_{\frac{1}{2}}$ = plasma elimination half life; h=hours; CL = systemic clearance

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Renally Impaired Subjects

Although the renal excretion of inactive omeprazole metabolites is decreased in patients with renal impairment, there is a compensatory increase in the capacity to eliminate these products through alternative routes, such as in the bile. Because omeprazole is completely metabolized by the liver before being excreted in the urine, it is predicted that the pharmacokinetics of the parent compound will remain substantially unaltered in the face of renal impairment. This has been born out empirically in patient studies (see Table 27). Theoretically, renal impairment could play a role in the clearance of other drugs or their metabolites which participate in drug-drug interactions with omeprazole.

Elderly Subjects

As part of the physiologic effects of aging both hepatic and renal functions diminish. High clearance drugs are subject to more profound changes in elimination rates compared to low clearance drugs. Based on the observation that omeprazole is a low-medium clearance drug, the sponsor has predicted that the physiologic effects of aging on hepatic clearance will be modest. This has been confirmed in studies of the pharmacokinetic properties of the drug in the elderly (see Table 27). In healthy geriatric volunteers (average age of 76) the mean plasma elimination half-life of omeprazole was 1 hour,

compared to 0.7 hours in young healthy subjects. In addition the mean AUC was two-fold higher in the elderly. These results have suggested to the sponsor that dose adjustments in geriatric patients are unnecessary both for the prescription and OTC formulations of omeprazole. An analysis of the common AEs listed in the SafeTNet database has shown that the profiles and rates of omeprazole related side effects are comparable between the elderly and younger patients. Similarly, both profiles and incidence rates of side-effects in the safety database from the 34 clinical trials that have been conducted worldwide to study the prescription formulation of omeprazole are comparable between age groups.

'Slow-Metabolizers' of Omeprazole

As discussed above, the cytochrome P450 isoform which is predominately responsible for the metabolism of omeprazole is CYP2C19. This isoform is polymorphically expressed in the human population. Amongst 3% of Caucasians and 15% of Asians CYP2C19 levels are negligible. These 'slow-metabolizers'(SM) manifest plasma elimination half-lives of omeprazole which are longer than in individuals who are rapid or 'extensive-metabolizers' (EM). The consequence of this difference is that the former group of individuals manifest a higher 24 hour median intragastric pH and longer intervals per 24 hours in which intragastric pH is greater than 4. Importantly, among SM/EM heterozygotes (30% of the Caucasian population), both the median intragastric pH (5.5 pH units) and intervals during which intragastric pH is higher than 4 (72.4% of a 24 hour period) are longer than in EM/EM homozygotes (3.1 pH units and 37.1% of a 24 hour period, respectively). Moreover, in SM/EM heterozygotes treated with omeprazole once daily, who are H. Pylori positive, plasma gastrin levels are more pronounced than in infected EM/EM homozygotes. This finding raises the spectre that pharmacodynamic and serum gastrin responses to standard doses of omeprazole are genetically determined and are significantly heterogeneous. The sponsor has argued that because the dosing interval is longer than the elimination half-life in SM/SM individuals accumulation of drug would be negligible. However, the sponsor has not fully addressed the diversity of response phenomenon that is based on empirical pharmacodynamic measurements. The sponsor has argued that in individuals who are SM/SM homozygotes, the potential of drug-drug interactions between omeprazole and other agents which are metabolized by CYP2C19 is negligible. For example, the clearance of diazepam, which in 'rapid-metabolizers' is decreased by approximately 25% during treatment with 20 mg omeprazole once daily, is not altered in 'slow-metabolizers'. However, CYP1A2, another cytochrome P450 isoform, may play a significant role in the metabolism of caffeine, phenacetin and theophylline in these individuals. The activity of this isoform is differentially induced by omeprazole treatment in 'slow-metabolizers'. It has been observed that administration of 40 mg omeprazole enhances the metabolism of caffeine by 30%. Currently, there is no data to support concerns about the potential for significant interactions between omeprazole and theophylline, a drug with a narrow therapeutic index whose blood levels must be carefully regulated in the treatment of asthma and chronic obstructive lung disease. Despite the absence of data to support the presence of drug-drug interactions between omeprazole and other agents, it is conceivable that subsets of genetically susceptible individuals who express distinct combinations of

cytochrome P450 isoforms may be identified in future studies. The absence of a learned intermediary in an OTC setting is expected to blunt recognition of such drug-drug interactions.

Pediatric Subjects

Currently, omeprazole is not indicated for prescription use in pediatric patients in the US. Despite the non-approved status in this age group the prescription formulation the sponsor is seeking approval for OTC use in children — of age or older. Based on an IMS Health national prescription audit, of the total number of prescriptions of omeprazole dispensed in the US, the projected use in the 11 year old to 20 year old age range is — Compared to the adult population, this usage is relatively small. However, in absolute terms, there is a substantial number of adolescent patients who have been exposed to omeprazole. Currently, there is a relative paucity of safety information about omeprazole exposure in this age group. In the past, almost all the clinical studies of the prescription formulation have excluded pediatric patients, including adolescents under the age of 18 years. As an exception, only 2 studies have been performed by the sponsor which included 74 pediatric patients, mostly small children and infants, with GERD. In the OTC arena, 100 adolescent subjects were administered doses of 20 mg omeprazole in 'actual use' studies in which the labeling indicated not to exceed 10 continuous days of dosing. In these studies, amongst those individuals who self-medicated with omeprazole in order to prevent heartburn anytime, 58% exceeded the 10 day limit of drug administration. In the post-marketing database of world-wide serious and US non-serious AE reports submitted by the sponsor information from a total number of 39 adolescent patients with 1 or more AEs was presented. This represents an extremely small databank of information from which to analyze the safety profile and detect 'signals' of omeprazole-linked toxicity in this age group. Because there may be age-related susceptibility to toxicity caused by long-standing hypergastrinemic responses to chronic administration of the drug (see below), it is apparent that the safety database is inadequate to draw firm conclusions about the relative safety of omeprazole in adolescents.

Use in Pregnancy

Currently, omeprazole is listed as a Pregnancy Category 'C' drug. The rationale for this assignment has been based on the observation that the drug induces embryo-fetal lethality in rabbits and post-natal body weight gain in rats. Reproductive toxicology studies, however, have indicated that omeprazole does not affect fertility and is not teratogenic. In the clinical arena, omeprazole has been used off-label to treat heartburn associated with pregnancy. Currently, in the US approximately — of omeprazole prescriptions are for females of childbearing age (15-45 years old). For combined years 1996 thru August 1999 the estimated prescription use in this subset of the population is —— A search of the MedWatch spontaneous reporting databank for all congenital abnormalities associated with omeprazole yielded 18 unduplicated congenital anomalies. These included 5 cases of anencephaly worldwide, of which one was in the US. Based on the number of new prescriptions among women between 15 and 44 years old and the

expected background rate of anencephaly in the US (0.36 per 1,000 births), it does not appear that there is an excess of this defect in omeprazole users. Likewise, since major defects affect approximately 3%-4% of live born infants, there does not appear to be excessive drug-related teratogenic effects associated with this drug (Ray Alderfer, MD, MPH, MO, Epidemiology Branch, HFD-733). Attached to these findings are a number of epidemiologic studies which have revealed no increased risk to the fetuses of pregnant omeprazole users. Based on these observations the sponsor has submitted a separate labeling supplement to the prescription formulation NDA (NDA 19-810/S-058) to support a change in the pregnancy category assignment for omeprazole from 'C' to 'B'. To further explore safety issues associated with pregnancy for OTC omeprazole a series of reviews will be submitted by the Division of Epidemiology and Surveillance. Based on the accumulated experience, to date there does not appear to be a significant teratogenic effect associated with omeprazole. The implications of fetal exposure to the drug for long-term post-natal development and risk for the development of diseases in later life has not been fully addressed. Such questions can only be addressed by properly designed prospective or nested control cohort studies. The sponsor has proposed the following wording in labeling for OTC omeprazole use: 'If pregnant or breastfeeding ask a health professional before use. May cause damage to your unborn or nursing child.' This wording does not address the scenario in which an individual becomes pregnant while using omeprazole. *In the OTC arena a labeled warning to avoid pregnancy it does not provide a sufficient 'safety net' to prevent exposure to drugs which are toxic to human fetuses. An adequate safety profile of omeprazole in pregnancy is mandatory to ensure adequate protection of the American consumer. In this respect, if omeprazole is not eligible for a Category 'B' status because of significant safety concerns for the unborn fetus, it would be difficult to justify its approval for OTC use.*

ADVERSE EVENTS ASSOCIATED WITH LONG-TERM ADMINISTRATION OF OMEPRAZOLE (more than 12 weeks total use)

Safety issues linked to long-term treatment with omeprazole (greater than 12 weeks, either continuous or intermittent administration) that have been identified include:

- Potential of omeprazole to mask underlying diseases including Barrett's esophagus, dysplasia and esophageal and gastric adenocarcinoma
- Serum gastrin levels and ECL changes
- Fundic gland polyps
- Colorectal adenomatous polyps and adenocarcinoma
- Atrophic gastritis, progression to intestinal metaplasia, dysplasia and gastric adenocarcinoma. data addressing the safety profiles and risk of gastrointestinal cancer have been presented.
- Genotoxic potential of omeprazole
- Potential of omeprazole to induce rebound of gastric acid secretion.

Most of these sections will include an overview of the clinical studies, post-marketing experience and reviews of the relevant worldwide literature.

Masking of Disease

Concern has been raised about the potential of omeprazole to mask symptoms of serious diseases which include Barrett's esophagus with dysplasia, esophageal carcinoma and gastric malignancy. As described above, amongst the cases of gastric adenocarcinoma linked to omeprazole treatment that have been reported voluntarily in the post-marketing phase to the SafeTNet databank there are a few cases in which treatment with the PPI led to a substantial delay of a number of months in the performance of diagnostic endoscopy. The sponsor has correctly pointed out in the NDA submission that in the context of chronic heartburn associated with GERD the presence of *'alarm symptoms'* necessitate immediate referral to a physician for endoscopic diagnosis. These symptoms include:

- Dysphagia and odynophagia
- Symptoms that are persistent, even during treatment
- Hematemesis, melena, rectal bleeding or anemia
- Weight loss and/or anorexia

The absence of such an instruction in the proposed OTC labeling is a matter of concern, since it has been established that

- a significant percentage of study subjects enrolled in the 'actual use' studies that have been performed who have self-medicated in order to prevent heartburn have not followed the instruction not to exceed 10 continuous days of treatment with omeprazole
- the pharmacokinetic/pharmacodynamic characteristics of omeprazole which are characterized by an approximately two day delay from the beginning of treatment until maximal acid suppression is reached and a relatively long duration of action make this drug an attractive choice for chronic or intermittent therapy for extended periods of time to prevent recurrent symptoms.

Moreover, there is a high recurrence rate of heartburn symptoms after cessation of therapy (see Figure 10). For these reasons, it is especially important to ensure that patients with chronic symptoms who will self-medicate for heartburn with agents that are available over-the-counter will be appropriately warned when empirical treatment in the absence of physician referral and diagnostic testing is inappropriate. The sponsor has correctly pointed out that in a large undifferentiated population of individuals who suffer from reflux symptoms or postprandial heartburn endoscopic studies reveal that most have negligible or benign and medically trivial mucosal changes, on endoscopic examination. Nonetheless, as alluded to in the introduction, a significant number of individuals with chronic heartburn have Barrett's esophagus or advanced stages of erosive esophagitis linked to significant potential to develop strictures in the absence of aggressive medical therapy. In addition, individuals rarely harbor dysplasia and/or adenocarcinomas.

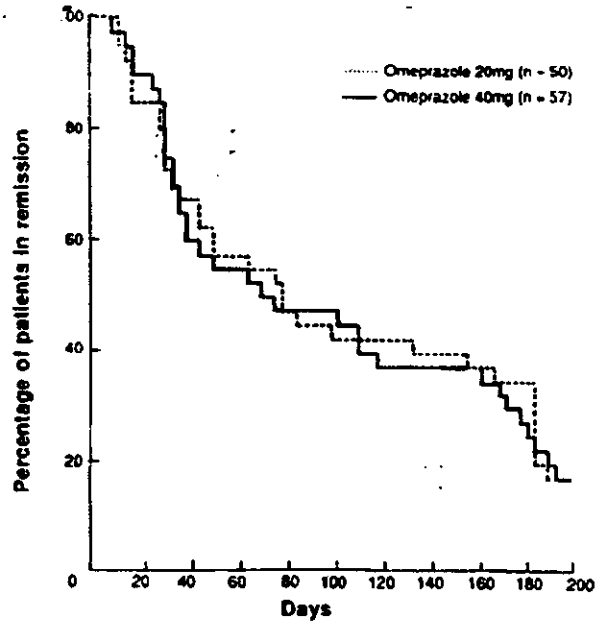

Figure 10. Cumulative relapse rate of esophagitis after complete healing with omeprazole. A total of 107 patients were completely healed with either 20 or 40 mg of omeprazole every day after which they were given no therapy. The initial dosage of omeprazole made no difference in the recurrence rate, and the populations are combined in this figure. (Modified from Hetzel, D. J., et al. Healing and relapse of severe peptic ulcer esophagitis after treatment with omeprazole. Gastroenterology 95:903, 1988. Copyright 1988 by the American Gastroenterological Association.)

Certain medically significant complications of GERD can only be diagnosed by endoscopic evaluation. Patient history plays an important role in the decision making process for triage by health care providers of patients. Important features that would be considered include the duration of heartburn symptoms and the presence/absence of accompanying symptoms.

According to current standards of medical practice in the United States and guidelines of the American College of Gastroenterology, patients with Barrett's esophagus should undergo regular endoscopic surveillance for the detection of dysplastic and/or pre-malignant changes. It needs to be emphasized that Barrett's esophagus or stricture, significant complications of GERD that require medical attention, are not necessarily related to the severity or frequency of heartburn. In the case of Barrett's esophagus, the frequency and severity of reflux symptoms among patients with this disorder compared to patients with uncomplicated non-erosive GERD are similar. Thus, both the qualitative and quantitative aspects of heartburn cannot differentiate between patients with this metaplastic and potentially premalignant condition and many patients with GERD.

A number of investigations have demonstrated that significant percentages of antacid users harbor either Barrett's esophagus or advanced stages of esophagitis[9] (see Table 28).

TABLE 28

Masking of Disease – Prevalence of Esophagitis, Barrett's Esophagus and Malignancies in Antacid Users with Heartburn (Endoscopic Studies)

Trial (Authors)	Number of patients	Mean duration of heartburn (years)	Number (%) of cases			
			Esophagitis (Grade II or greater)	Barrett's esophagus	Gastric cancer	Esophageal cancer
Corder AP et al.[5]	143	10	33 (15)	6	0	0
Robinson et al.[1]	155	11	73 (47)	9.0 (6)	0	0
Protocol SKF 92334/B0025[23,24]	208	9.6	5 (2.4)	2 (1.0)	0	0
Pappa KA et al.[22]	234	Minimum of 5 episodes per month	9 (3.8)	Not mentioned	0	0

In one study, 178 subjects with at least three months of frequent heartburn relieved by antacids who had symptoms for at least 4 of 7 days during the week prior to the study, were screened by upper endoscopy[10]. Of these patients 13 were excluded because of other baseline gastrointestinal diseases that included mucosal dysplasia, columnar metaplasia of the esophageal epithelium, adenocarcinoma and peptic ulcer disease, and ten other subjects because of ineligibility criteria. Of the remaining 155 subjects that were analyzed, 93% of the subjects rated their heartburn as moderate to severe, although less than half recorded daily heartburn. In the study, endoscopic evaluation revealed that 31% had mild esophagitis; however, 16% had more severe erosive esophagitis which in some cases included stricture. Importantly, 6% of the study subjects had non-dysplastic Barrett's esophagus; moreover, two subjects were excluded at the outset because of dysplastic mucosal changes. Because patients had heartburn for an average duration of 11 years it was concluded that:

> 'chronic heartburn can reflect a wide range of diagnostic findings including important underlying pathological features and they warrant a full medical examination to detect such abnormal conditions and to permit selection of appropriate therapy'.
>
> "long-term heartburn may warrant full medical examination to exclude important underlying pathological conditions and select appropriate treatment. The results

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[9] M. Robinson et al. Heartburn requiring frequent antacid use may indicate significant illness. Arch Intern Med 1998; 158:2373-2376.
AP Corder et al. Heartburn, oesophagitis, and Barrett's oesophagus in self-medicating patients in general practice. BJCP 1996; 50(5):245-248.
KA Pappa et al. Endoscopic findings in a target population for over-the-counter treatment of heartburn. Gastroenterology 1996; 106, 4(A):146.
Protocol SK&F 92334/B0025. An epidemiological study to establish the prevalence of endoscopically identified acid-peptic disorders in patients frequently taking antacids. NDA 20-238:158-166.
DB Burnham, CJ Fruednabm N Asbel-Sethi. The prevalence of endoscopic lesions in the upper gastrointestinal (UGI) tract of frequent antacid users. Gastroenterology 1993; 104(suppl4):A49.

[10] M. Robinson et al. (locus cited; 1998)

> of the current study and long-term users of antacids show that heartburn and other GERD symptoms may not be the trivial problem suggested by some consumer advertising. Physicians should understand that frequent and persistent GERD symptoms might reflect important gastrointestinal pathologic features"...

However, it was also concluded that:

> 'most individuals with occasional mild heartburn can be adequately and safely treated with life style modifications and OTC medications including antacids and low dose H_2 receptor antagonists'..

Recently, the 'GERD Management Group', a multidisciplinary team of physicians in family practice, general internal medicine, gastroenterology, and gastrointestinal surgery developed a consensus approach on the optimal medical management of GERD[11]. In the algorithm of patient management that they have proposed empiric therapy for symptoms that are typical of GERD only after exclusion of 'alarm' or atypical symptoms (see Table 29). Concepts incorporated into the algorithm include the following points:

- OTC antacids/low dose H-2 receptor antagonists in conjunction with life-style modifications are deemed appropriate as modalities of empirical treatment in the absence of a definitive endoscopic diagnosis
- With symptomatic relief, the initial empiric treatment regimen should be continued for up to 6 weeks, before a trial off medication
- Should symptoms recur, retreatment with the previous regimen should be instituted
- If symptoms persist after 6 weeks, higher doses of H-2 receptor antagonists or a PPI should be administered for up to an additional 6 weeks
- After this 'step-up' phase of treatment, a 'step-down' phase to the earlier regimen of low-dose H-2 receptor antagonists/antacids, etc. should be instituted. If symptoms recur, referral for endoscopy to make a definitive diagnosis and evaluate for GERD complications is indicated
- At any phase of treatment, including when heartburn first appears, if symptoms are atypical or suggest a serious non-GERD diagnosis prompt referral to a physician for diagnostic evaluation that usually includes endoscopy is appropriate.
- Upon endoscopic evaluation, a number of treatment options are available, depending on the lesions that are found. In the case of symptomatic non-erosive GERD and erosive esophagitis PPIs are often prescribed for maintenance treatment. In recalcitrant cases, anti-reflux surgery can be considered

[11] DO Castell et al. GERD: Management Algorithms for the Primary Care Physician and the Specialist. Practical Gastroenterology 1999; 20-42

TABLE 29

Early Referral Symptoms in Patients With Suspected GERD
• Dysphagia, odynophagia
• Early satiety
• Frequent vomiting
• Gastrointestinal bleeding
• Unexplained weight loss
Atypical Symptom of GERD
• Asthma
• Chronic cough
• Chronic hoarseness
• Nausea and Vomiting
• Unexplained chest pain

In summary, although empiric therapy with pharmacological agents which suppress acid in the gastric lumen is a recognized element in the management of patients with GERD, proper triage of certain individuals for prompt endoscopic evaluation and appropriate medical follow-up is required. One reason for immediate referral is the presence of 'alert symptoms'. This standard of care must be taken into account during adjudication of the suitability of PPIs in the OTC market if it is determined that patients with GERD will be among those who will self-medicate for heartburn.

Although people with these medically significant lesions that require early recognition and/or management by a physician represent a minority of undifferentiated patients with heartburn, the prospect that they would not be 'gated out' from the OTC check-out line at the pharmacy presents a disturbing scenario. The 'minimalist' OTC labeling that has been proposed for omeprazole does not bear adequate warnings for the identification of individuals at high risk for advanced lesions. In the current submission, the sponsor has strongly agreed with the need to recognize 'alarm symptoms' and has made the following statement:

> *... 'In order to avoid the risk of possible complications that may occur with long-standing and persistent heartburn, consumers should be made aware of the indications, dosage and duration of therapy of over-the-counter heartburn medications they intend to use. In addition, they should have a clear understanding of when to seek medical attention. This information should be clearly labeled with explicit instructions that are understandable by all potential users. The proposed labeling for over-the-counter omeprazole does instruct users to seek medical advice if they need to take the medication as directed continuously for more than 10 days...The label will also clearly highlight alarm symptoms that the presence of any of these additional symptoms must warrant prompt medical attention before continuing self-treatment' ...*

The statements by the sponsor correctly express one of the most significant caveats concerning the appropriate use of any empiric therapy for chronic heartburn. Unfortunately, the proposed labeling does not contain substantial information about the

'alarm symptoms' nor does it define in a specific way an appropriate endpoint of chronic self-medication. The phrase 'continuously for more than 10 days'.is ambiguous and may infer to some consumers the notion that chronic treatment is acceptable if subjects take a q10 day one-day 'holiday' from self-administration of omeprazole.

Consideration should be given to modify the proposed labeling to recommend individuals who suffer from chronic heartburn to self-administer omeprazole for a maximum period of 4-6 weeks in an OTC setting, if diagnostic endoscopy has not yet been performed. In conjunction with the formulation of clear instructions that define which individuals should immediately seek referral to a health care provider the sponsor should provide adequate efficacy information and new actual use studies to determine that there is strict adherence to the labeling.

Hypergastrinemia, ECL Cell Hyperplasia and Atrophic Gastritis

Because of growth promoting effects of omeprazole on the gastrointestinal mucosa, concern has been raised about the carcinogenic potential of long term administration of this drug to patients. Specifically, the Agency has sought to exclude pathophysiologic processes related to carcinogenesis in humans exposed to omeprazole for more than 1 year.

- First, there is a significant incidence of carcinoid (ECL cell) tumors of the stomach induced by long-term treatment of rats. In the oxyntic mucosa of adult humans and in all animal species tested, ECL hyperplasia is frequently induced by omeprazole. This phenomenon has been linked to the trophic effects of increased levels of circulating gastrin (endocrinological effects) that occur as a result of the suppression of acid secretion by the drug. In addition to endocrine, paracrine and even autocrine effects of gastrin have been postulated. Nonetheless, unlike the rat, there is no compelling evidence that drug-related ECL hyperplasia progresses to carcinoid tumors in adult humans.

- In addition, concern has been raised about the trophic effect of omeprazole induced hypergastrinemia on nongastric mucosa. In particular, attention has been directed to effects of omeprazole on epithelial cells in various organs. In cell culture, gastrin exerts trophic effects on non-ECL gastrointestinal cells (including colonocytes).

The chronicity and recurrence of symptoms which is characteristic of many heartburn sufferers and the demonstration of the frequent extension of continuous omeprazole usage beyond the labeled limit of 10 days that was observed in the 'actual use' OTC studies (review by Dr. L. Chin, M.D., MPH, OTC Division and Dr. David Shettig, M.D.) strongly suggest that a significant percentage of patients will self medicate on a chronic intermittent or continuous basis, irrespective of labeling instructions. It is critical that this prediction be taken into account in the formulation of a safety profile analysis of omeprazole usage in an OTC setting. A number of physiological consequences emanate from the chronic usage of omeprazole. One of these is the heightened secretion of gastrin as a consequence of long-term PPI therapy. Circulating gastrin released by G cells from

the stomach antrum has trophic effects, on enterochromaffin like (ECL) cells which secrete histamine, parietal cells which secrete acid, and other epithelial cells in the gastrointestinal tract. Gastrin release is controlled by a negative feedback mechanism that is sensitive to acid levels in the stomach. The extent of release of this hormone depends on a numbers of factors which include the size of the G cell mass, the degree and duration of acid suppression, the presence/absence of food in the stomach and the degree of antral distension. Due to the long duration of action of omeprazole and the profound suppression of acid secretion which occurs in many individuals treated with daily 20 mg doses, a two to fourfold rise in serum gastrin levels often occurs. In addition, there is a subset of individuals in which serum gastrin levels rise well above the upper limit of normal to levels greater than 400 pg/ml. Many patients with profound rises of serum gastrin levels while on omeprazole treatment are H. pylori positive and manifest histopathogical features consistent with chronic corpus atrophic gastritis. It is likely that in the face of reduced parietal cell function caused by H. Pylori in some individuals who are colonized with the organism, the degree of acid suppression induced by omeprazole is more pronounced than in non-infected individuals. H. Pylori infected individuals may be particularly susceptible to develop exaggerated secretion of gastrin during treatment with PPIs. As described above, gastrin release is stimulated by the suppression of acid. In this respect, exaggerated gastrin responses observed in some subjects treated with agents that suppress acid secretion is not limited to the pharmacological class of PPIs. High dose frequently administered H_2-blockers have also been shown to induce increased serum gastrin levels. However, because of the reversible nature of H_2 receptor blockade by these agents, low dose H_2-receptor antagonists administered once or twice a day, which are currently approved for OTC marketing, generally are not associated with this phenomenon. In contrast, because of their long duration of action and potency full-dose PPIs that are indicated for the treatment of active ulcer disease (eg omeprazole 20 mg qd) induces elevated serum gastrin levels in some individuals. Concerns raised about the potential of high circulating levels of gastrin to induce tumors have been raised emanate from the following observations:

- ECL cell carcinoids develop both in male and female rats treated for 24 months with daily doses of omeprazole, in a dose-related matter.

- In studies involving more than 200 patients serum gastrin levels increased during the first 1-2 weeks of once daily administration of therapeutic dosages of omeprazole, in parallel with inhibition of acid secretion. Immediate increases of serum gastrin levels induced by 20 mg doses of omeprazole were higher than those induced by full doses of H_2-receptor antagonists that are indicated in the treatment of peptic ulcer disease, (range increases were 1.3 - 3.6 fold vs 1.1 - 1.8 fold, respectively). Gastrin values returned to pretreatment levels usually within 1-2 wks after discontinuation of therapy.

- Gastric carcinoids are also linked to two conditions associated with chronically elevated serum gastrin levels. These include Zollinger-Ellison Syndrome (ZES) which is a component of Multiple Endocrine Neoplasia I (MEN-1) and gastric body predominant chronic atrophic gastritis (CAG). Carcinoid tumors associated with

elevated serum gastrin levels are not as invasive as those that develop in the presence of normal serum gastrin levels and normal oxyntic gastric mucosa. Generally, their growth is hormone-dependent and they are amenable to treatment by local excision. Although many patients on long-term PPI therapy manifest a 2-4 fold increase in gastrin levels there are a small number of individuals who develop greater than 4-fold increases in serum concentrations of the hormone, above baseline. Although elevated serum gastrin levels have been associated ECL cell hyperplasia in humans, currently there is little empirical evidence that they induce carcinoids or other malignancies.

- It has been postulated that raised serum gastrin levels may be risk factor for the development of colorectal adenocarcinoma. Studies examining serum gastrin levels in patients with colorectal adenomas and adenocarcinomas, compared to individuals without these lesions, have produced conflicting findings[12]. These investigations are limited because of their retrospective, case control study designs. In some of the studies, mean serum concentrations were elevated only in a small subset of patients with colorectal neoplasms. The mixed results of the studies suggest that it will be necessary to perform trials with prospective study designs to definitively determine whether there is a causal link between elevations of serum gastrin and these lesions, particularly since patients with pernicious anemia, post-truncal vagotomy and/or gastric surgery, CAG or ZES who have longstanding hypergastrinemia have not been observed to have an increased risk to develop colorectal cancer.

Numerous reports in the literature have demonstrated an association between the use of omeprazole and fundic gland polyps. Although the pathogenesis of these benign lesions is unknown they have negligible malignant potential. Histopathologically, they are comprised of hyperplastic gastric epithelial cells and cystic glandular structures. Because parietal cells bear gastrin receptors, it is likely that omeprazole-stimulated increases in serum gastrin concentrations lead to parietal cell hypertrophy.

- A possible carcinogenic mechanism that has been proposed is that omeprazole administration may cause a tumor enhancing effect in patients who are infected with *H. pylori*. The organism has been found to play an etiological role in the pathogenesis of a number of conditions in the stomach. These include chronic atrophic gastritis, which when associated with intestinal metaplasia (types II and III), is considered to be precursor lesions in a multiple step neoplastic process that leads to gastric adenocarcinoma. H. Pylori stimulates gastrin release by the antral 'G' cells. This may occur because the organism induces a reduction in somatostatin secretion by 'D' cells. In the presence of *H. pylori* infection, proton pump inhibitors have been found to accentuate inflammation of the oxyntic (corpus)

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[12] M Orbuch et al. Prolonged hypergastrinemia does not increase the frequency of colonic neoplasia in patients with Zollinger-Ellison syndrome. Dig Dis Sci 1996 Mar; 41(3):604-613.
CM Thorburn et al. Gastrin and colorectal cancer: a prospective study. Gastroenterology 1998 Aug; 115(2):275-280
JF Seitz et al. Elevated serum gastrin levels in patients with colorectal neoplasia. J Clin Gastroenterol 1991 Oct; 13(5):541-545
H Graffner et al. Omeprazole-induced hypergastrinemia does not influence growth of colon carcinoma. Dig Dis Sci 1992 Apr; 37(4):485-489

mucosa. A question has been raised as to whether drug-linked accentuation of the inflammatory process and an increase in gastrin stimulation may promote the risk for progression to Types II and III intestinal metaplasia, and eventually dysplasia and adenocarcinoma.

It is estimated that 1% of individuals with H. Pylori induced chronic gastritis will eventually develop gastric adenocarcinoma. Since the organism is classified as a Group I carcinogen by the World Health Organization, concern has been raised whether PPI treatment promotes dysplastic transition of the infected gastric mucosa. A study by Kuippers et al concluded that long-term treatment with omeprazole hastened the development of atrophic gastritis in H. Pylori positive patients. This investigation was limited since it was not a randomized, controlled trial and the two cohorts that were compared were from different countries and were characterized by mean ages which were nine years apart. Other published trials in patients with atrophic gastritis prior to pharmacological acid suppression who were then placed on long-term omeprazole treatment for up to 8 years have not revealed progression of the inflammatory process. In two studies which reported an increase in the prevalence of atrophic gastritis in individuals treated with omeprazole, the H. Pylori status of patients was not consistently determined. Thus, it can be concluded that even if omeprazole causes histopathologic progression to intestinal metaplasia not associated with dysplastic changes (Type I) in the stomach, there is no convincing evidence that a causal relationship exists between administration of the PPI and further progression to Types II and III intestinal metaplasia, associated with dysplasia or adenocarcinoma. Acceleration of atrophic gastritis in H. Pylori positive individuals treated long-term with PPIs was addressed by a FDA Advisory Panel[13]. After a discussion surrounding the data which was available at that time the committee concluded that there was not convincing documentation of an increase in atrophic gastritis or intestinal metaplasia in patients on prolonged PPI therapy to warrant a recommendation that H Pylori infection should be eradicated prior to prescribing long-term PPI therapy. Because of lingering uncertainty, the FDA requested an update of information from the sponsor that was submitted on June 17, 1999.[14] The update included clinical study data, an updated review of the medical literature and an analysis of the world-wide safety database (SafeTNet) through December 31, 1998. This submission has been reviewed separately (NDA 19-810/S061; MO reviewer Mark Avigan, MD CM). Information from that submission has been incorporated into the analysis discussed below.

Long-term Clinical Trials

The sponsor has provided information gathered from 2 US and 4 non-US trials encompassing approximately 1,100 patients treated with study medication for time periods ranging between 2 and 14 years (see Table 30).

[13] GI Drugs Advisory Committee Meeting held on Nov 4, 1996
[14] NDA 19-810; Prescription formulation of omeprazole for GERD

TABLE 30
INTEGRATED SUMMARY OF SAFETY – LONG-TERM TREATMENT
TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED

TRIAL NO./ LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
Astra Merck #016 US [64]	TRIAL DESIGN: A double-blind multi-center parallel group trial OBJECTIVE: To determine whether long-term therapy with omeprazole or an H_2-antagonist will alter the natural course of Barrett's esophagus and result in regression of the area of esophageal involvement COMPLETION DATE: 4/94	TRIAL DURATION: 24 months 1. Omeprazole 40 mg bid for 12 months then 20 mg bid for another 12 months 2 Ranitidine 300 mg bid for 24 months Total.	 57 49 106	Serum gastrin, gastric/esophageal biopsy (with histologic assessments of ECL cells and presence or absence of atrophic gastritis and intestinal/esophageal metaplasia) at baseline and every six months; colonoscopy for evaluation of colon polyps at baseline and 24 months; and overall clinical safety assessments. The number of patients with at least one endoscopy performed ≥ six months after baseline was 53 in the omeprazole group and 44 in the ranitidine group.

TABLE 30 (continued)
INTEGRATED SUMMARY OF SAFETY – LONG-TERM TREATMENT
TABLE OF LONG-TERM CLINICAL TRIALS REVIEWED

TRIAL NO./ LOCATION	TRIAL DESIGN AND OBJECTIVE	TREATMENT GROUPS	NUMBER OF PATIENTS RANDOMIZED	ASSESSMENTS PERFORMED
Astra Merck #017 US [76]	TRIAL DESIGN: A double blind, randomized, multi-center group trial conducted in three phases OBJECTIVE: To investigate the efficacy of 2 oral doses of omeprazole vs. placebo in the maintenance treatment of patients with active duodenal ulcers healed by omeprazole; to evaluate the long-term safety of omeprazole	TRIAL DURATION: 24 months Phase 1: (4 weeks) 20 mg omeprazole qam open label Phase 2: (weeks 1-52) 1. Omeprazole 20 mg od 2. Omeprazole 10 mg od 3 Placebo Phase 3: (weeks 53-104) 1. Omeprazole 20 mg od 2. Omeprazole 10 mg od 3. Placebo	1,170 362 378 179 170 138 27	Endoscopy was performed at baseline, weeks 4, 6, 26, 52, and 104. Gastric fundus biopsy for histologic assessments of ECL cells was performed at baseline, weeks 4, 52 and 104 Serum gastrin was performed at baseline, week 4, 26, 52 and 104 Overall clinical safety assessments were also performed Note: 335 patients completed Phase 3 138 in omeprazole 10 mg; 170 in omeprazole 20 mg and 27 in placebo groups respectively
Astra Hassle #1-665 Netherlands [75]	TRIAL DESIGN: Randomized, double-blind, double dummy, parallel group design. OBJECTIVE. To compare the effects of the different treatments on histological parameters and parameters of premalignant change in Barrett's epithelium and relate these to the degree of acid gastro-esophageal reflux. COMPLETION DATE: 4/96	TRIAL DURATION: 24 months 1 Omeprazole 40 mg bid 2 Ranitidine 150 mg bid 3. Open label Omeprazole 40 mg bid Total:	33 35 4 72	Gastric biopsies were taken at the first and last visit for histologic assessments of ECL cells and gastritis status, including activity, inflammation and atrophy. Serum gastrin was evaluated at baseline and at 3, 9, 15 and 24 months. *H. pylori* status was determined by serum IgG. Overall clinical safety assessments were also performed Note: 26 patients completed in the omeprazole group and 27 patients completed in the ranitidine group.
Astra Hässle #1-635 Scandinavia [72]	TRIAL DESIGN: Open, parallel group trial OBJECTIVE: To compare omeprazole treatment with surgical treatment (anti-reflux surgery) in long-term management of peptic esophagitis COMPLETION DATE: Interim data from 36 months - 1997	TRIAL DURATION: 60 months (Data included here is from an interim report after 36 month). Patients who had recurrent erosive or ulcerative esophagitis and were suitable candidates for surgery were healed with omeprazole 20 or 40 mg daily. Healed patients were then randomized to: 1. Omeprazole 20 mg daily 2. Anti-reflux surgery	155 155	Endoscopies with gastric biopsies were performed at baseline, 12 and 36 months *H. pylori* status was determined by biopsy Histologic assessments of ECL cells and gastritis status, including activity, inflammation and atrophy were evaluated Serum gastrin levels were performed at baseline, 12 and 36 months Overall clinical safety assessments were also performed Note: 139 omeprazole patients completed 36 months of treatment and 130 patients in the anti-reflux group completed 36 months of the study.
Astra Hässle #1-548/614 Germany, Netherlands, Canada, Australia [73]	TRIAL DESIGN: Open label treatment OBJECTIVE: To document the efficacy and safety of omeprazole in the long-term treatment of patients with severe peptic ulcer (1-548) and reflux esophagitis (1-614) disease who were refractory to treatment with H_2-receptor antagonists and ineligible for surgery. (This was a *Compassionate Use Study* since no maintenance indication was approved) Original study was designed for 5 years and patients were asked to extend COMPLETION DATE: 4/97	TRIAL DURATION: *60 – 144 months* Phase 1 (healing phase) 4-8 weeks: Omeprazole 40 mg bid (open label) Phase 2 (prophylaxis phase) over 11 years: Omeprazole 20 mg every morning (dosing of up to 80 mg could be used in cases of recurrence)	Total of 265 patients: 73 treated for 0-5 yrs 173 treated for 5-10 yrs 19 treated for 10-12 yrs	Endoscopy with gastric biopsy and histologic assessments of ECL cells and gastritis status, including non-atrophic, sub-atrophic or atrophic gastritis were performed annually Serum gastrin levels were performed annually. *H. pylori* status was also determined by biopsy. Overall clinical safety assessments were also performed Note: 70% of patients were followed for more than 5 years. 133 patients withdrew from the study for various reasons.

In this database more than half the patients were treated in an open-label fashion. Conditions that were being treated included Barrett's esophagus, severe and recurrent erosive or ulcerative esophagitis and severe peptic ulcer disease, patient populations with conditions which are distinct from those who have been proposed for OTC market. Findings of these trials included the following:

- Only a minority of patients developed serum gastrin concentrations exceeding 400 pg/ml. When categorized by H. Pylori status serum gastrin levels over 400 pg/ml were observed only in H Pylori positive individuals.
- Greater increases in serum gastrin concentrations were noted in the omeprazole treated group compared to the group treated with ranidine.

These findings are demonstrated in Trial 016 as follows:

- After 24 months between 51% and 69% of patients treated with omeprazole 40 mgs qd for 12 months followed by 20 mgs qd for 12 months manifested increases in serum gastrin concentrations of more than 40 pg/ml. In contrast, between 18% and 28% of patients treated with ranitidine 300 mg bid for 24 months. At the end of treatment the highest serum gastrin concentrations were observed in 3 patients (7%) in the omeprazole-treated group. These patients manifest gastrin levels ranging from 250 pg/ml to less than 400 pg/ml.
- In trial 017 median gastrin concentrations increased moderately with omeprazole treatment (3 open-label phases - 20 mg qd for 4 weeks; followed by 20 mg or 10 mg od for 1 year; followed by 20 mg or 10 mg od for 1 year). Few patients developed serum gastrin concentrations in excess of 150% of the upper limit of normal.
- In trial I-665 (omeprazole 40 mgs bid vs ranitidine 150 mgs bid; followed by open-label omeprazole 40 mgs bid) serum gastrin levels of greater than 400 pg/ml occurred in patients who were H. Pylori positive.
- In trial I-635 patients in the omeprazole treatment group (vs the anti-reflux surgery group) had greater increases in serum gastrin concentrations. These rarely exceeded 100 pmol/l.
- In trial I-548/614 two H. Pylori positive patients developed marked increases in serum gastrin concentrations between baseline and year 5 measurements (430 pg/ml to 6,320 pg/ml and 173 pg/ml to 9,650 pg/ml). In conjunction with H. Pylori infection these individuals developed severe chronic corpus atrophic gastritis

In summary, the presence infection has been observed to accentuate rises in omeprazole-induced serum gastrin concentrations. In some 'outlier' individuals rises in gastrin levels induced by omeprazole 20 mg per day are pronounced reflecting H. Pylori associated reduction in parietal cell function. The trophic effects of longstanding hypergastrinemia on ECL like cells and other gut epithelial cells (eg colonocytes) are not fully known. With the information at hand it is not possible to absolutely exclude the possibility that this mechanism may promote malignancy in some individuals. Whether omeprazole plays a role in promoting transition from early to late stages of gastritis or

dysplasia/malignancy is not clear. Further prospective and/or nested cohort studies are necessary to answer this question.

ECL Cell Changes Evaluated During Long-term Clinical Trials of Omeprazole in Adults

It is well established that omeprazole and other PPIs induce the benign hyperplasia of ECL cells. A review of the clinical trials has established that omeprazole treatment for 24 months or longer was associated with the induction of simple, linear or micronodular forms of hyperplasia. No cases of dysplasia or carcinoid tumors were observed, with one exception. In trial 017, one case of carcinoid was reported during the study period. This was analyzed to be a preexisting condition.

Colonic Epithelial Cell Changes Evaluated During Long-term Clinical Trials of Omeprazole in Adults

In Trial 016 (treatment duration - 24 months) with colonoscopic assessment of colorectal polyps greater than 3mm in diameter at baseline and after treatment, no substantial differences in polyp numbers between the omeprazole and ranitidine treatment groups were observed. Similarly, there were no meaningful differences between the treatment groups when patients were stratified at baseline according to polyp numbers and then grouped according to the number of polyps that were identified at the end of treatment (After the two year treatment phase, when patients were grouped according to the polyp histopathologic type, no meaningful differences were discerned between the omeprazole and ranitidine treatment groups

Fundic Gland Polyps During Long-term Clinical Trials of Omeprazole in Adults

Clinical studies to investigate the relationship between fundic gland polyps and treatment with omeprazole have not been provided. However information has been accumulated from the post-marketing databank and literature (see below).

Atrophic Gastritis and Gastric Cancer Risk Evaluated During Long-term Clinical Trials of Omeprazole in Adults

As alluded to above, advanced atrophic gastritis with intestinal metaplasia is associated with an increased risk for adenocarcinoma. Controversy exists whether H. Pylori infection hastens the development of this lesion, best characterized by true gland atrophy in the corpus of the stomach. In the six long-term clinical studies, described above, there were no patients who developed gastric dysplasia or adenocarcinoma. In study 017, at baseline, only four patients developed histopathologic characteristics of atrophic gastritis. After two years of omeprazole treatment (10 mg or 20 mg daily doses) the number of patients with atrophic gastritis increased to 13. No case of intestinal metaplasia or dysplasia were recorded. In Trial I-665, after 24 months of treatment, 3 patients who were administered omeprazole and one who was administered ranitidine developed moderate atrophy of the corpus mucosa. All of these patients were H. Pylori positive. In

Trial I-635, as in the other studies, corpus gastritis activity was confined to patients who were H. Pylori positive. In the study the administration of omeprazole did not impact on the degree or rate of mucosal atrophy compared to treatment with surgery alone. In Trial I-548/614 an annualized incidence rate of mucosal atrophy was observed to be 4.0% in H. Pylori positive patients and 0.7% in H. Pylori negative patients. Similar to the results listed above, in Trial I-565 there was little apparent change in the activity of corpus gastritis in patients who were H. Pylori negative, irrespective of treatment with omeprazole. However, in the H. Pylori positive group there was an increase in the severity of gastric mucosal atrophy noted in some patients. No patients developed mucosal dysplasia or adenocarcinoma. From this relatively small patient database, it is apparent the predominant factor that impacts on the evolution of corpus gastritis to atrophy is the presence of H. Pylori infection. The evidence suggests that long-term treatment with omeprazole does not slow this process. On the other hand, there is little evidence to support the contention that omeprazole treatment hastens the process that leads to atrophy, dysplasia or adenocarcinoma. It is important to exclude this possibility since if omeprazole treatment augmented the risk of H. Pylori infected individuals to develop adenocarcinoma, then a strong case could be made that eradication of the organism with combination antibiotic therapy should precede long-term treatment with PPIs. Further controlled studies to definitively answer this question are still needed.

Neoplastic and Hyperplastic Changes of Gut Mucosal Cells Associated with Omeprazole Reported During Post-marketing Safety Surveillance

In another submission, which was reviewed separately (sponsor's response to the Agency's communication regarding an earlier pediatric written request; submitted August 4, 1999) the sponsor has catalogued adverse events reported to the Worldwide Adverse Event Database (SafeTNet). Amongst the list of events were reports of ECL cell hyperplasia and other gastro- intestinal epithelial cell abnormalities linked to use of the drug through June 30, 1998.

Of 22 reports of ECL cell hyperplasia, 10 were not attributable to underlying gastrinomas, pernicious anemia or atrophic gastritis. In addition, of 21 reports of gastric or duodenal carcinoids, 6 could not be attributed to gastrinoma or pernicious anemia. From this information, it is not possible to fully exclude a potential for drug-induced chronic hypergastrinemia to induce carcinoid tumors in a small percentage of omeprazole treated patients. The true incidence of such an association appears to be very small.

Of a total of 73 reports of benign gastric or duodenal polyps there were 3 reports of duodenal adenomatous polyps. Adenomatous polyps of the stomach and duodenum are neoplastic and have the potential to progress to malignancy. Of concern is the relative rarity of spontaneous duodenal adenomas in the absence of Familial Adenomatous Polyposis/Gardner's Syndrome. In the post-marketing surveillance of omeprazole there have been a total of 38 reports of definite or possible colorectal carcinomas and 49 cases of gastric adenocarcinomas. A detailed characterization of these cases was not initially presented by the sponsor. To further characterize these omeprazole-associated cases of

neoplasia obtained from the post-marketing database, the agency requested that the sponsor submit detailed case narratives (see below).

To address concerns raised about the carcinogenic potential of omeprazole in humans, the Agency issued an Information Request Letter to the sponsor on 12/14/99 requesting the following documents:

- Case report forms for patients enrolled in Study 016 who developed skin cancer or other neoplasms
- Case report forms for patients enrolled in Study 016 who developed gastrointestinal polyps with inclusion of histopathologic information as well as a description of their site, size, number, and distribution
- Case report forms for patients who had gastrointestinal carcinoids, adenomas, or carcinomas from four long-term treatment trials that include: a) Study I-665 ('Effects of elimination of gastro-esophageal reflux by omeprazole on parameters of premalignant change and dedifferentiation'), b) Study I-635 ('Omeprazole versus anti-reflux surgery in the long-term management of peptic esophagitis –a Scandinavian comparative multicenter study'), c) Study I-548/614 (' The compassionate use of omeprazole in patients with peptic ulcer disease or severe erosive esophagitis, not responding to treatment with histamine-2 receptor antagonists and ineligible for surgical treatment'), and d) Study I-565 ('Efficacy and safety of omeprazole in long-term treatment of patients with peptic ulcer or esophagitis resistant to treatment with ranitidine')
- Adverse reaction reports from post-marketing surveillance for gastrointestinal carcinoids, adenomas, or carcinomas (all segments of the gastrointestinal tract)

From the information that has been provided it is apparent that 7 patients enrolled in Study 016 developed malignant neoplasms, including 5 in the omeprazole treatment arm and 2 in the ranitidine treatment arm. In the omeprazole treatment arm, the cases included 2 basal cell and 1 undefined cancer of the skin, 1 prostate cancer and 1 breast cancer. In the ranitidine treatment arm, the cases included 1 adenocarcinoma of the lung and 1 basal cell cancer. From this small series, it is not possible to attribute causality to the use of drug. In the same study, colonoscopic surveillance revealed colonic polyps in 30 patients in the omeprazole treatment arm and 26 patients in the ranitidine treatment arm. Of the total number of subjects who were surveillanced at the end of the study, there was an almost identical number in each group who developed histopathologically proven adenomas (7 in the omeprazole treatment arm and 10 in the ranitidine treatment arm). In addition, there were no apparent differences in the incidence and rate of growth (size) of colonic polyps in the two study arms.

A composite of the submitted post-marketing surveillance adverse reaction reports of gastrointestinal neoplasms in patients being treated with omeprazole includes the following:

- 32 cases of carcinoid tumors of the stomach and/or duodenum. Of these, based on information that has been provided, at least 13 were not attributed to the presence of gastrinoma(s) due to ZE or MEN syndromes or other conditions. Of the carcinoids not attributable to gastrinomas, 9 were gastric and 4 duodenal.
- 29 cases of gastric adenomas.
- 3 cases of duodenal adenomas. None of these patients was reported to have a hereditary polyposis syndrome and all were medicated with omeprazole for 7 months or longer.
- 22 cases of colonic adenomas.
- 12 cases of esophageal carcinoma, many who had underlying risk factors such as Barrett's esophagus.
- 49 cases of adenocarcinoma of the stomach. In at least 4 of these cases, omeprazole therapy caused masking of symptoms and/or temporary healing of the gastric mucosa with a 1 to 12 month delay in the diagnosis of malignancy.
- 1 case of duodenal adenocarcinoma.
- 31 cases of carcinoma of the colon.
- 18 cases of GI anatomic site not specified.

The sponsor has provided some safety information concerning the long-term use of omeprazole. Safety data from a two-year study (Study 016) of patients with Barrett's esophagus treated either with omeprazole or an H_2 antagonist were analyzed. As an outcome of this analysis the sponsor has concluded that there are "no significant differences between treatment groups observed in the development of ECL cell hyperplasia, corpus atrophic, gastritis, corpus intestinal metaplasia or colon polyps exceeding 3 mm in diameter." It is apparent that the sponsor's submission is characterized by significant limitations with regards to the Agency's strong interest to ensure the safety of long-term usage of Omeprazole. These limitations include the following:

- The submitted study was small. Of a total of 57 patients randomized to receive omeprazole only 46 completed the two year study. This small N- value precludes a comprehensive safety analysis and detection of adverse events which may not be very common.
- Patients in Study 016 were tracked for only two years. Because of the potential for a lag in drug-related effects associated with omeprazole, results of the study do not preclude long-term growth related effects of omeprazole in the G.I. tract and other organs.
- The sponsor has not submitted information about the safety of omeprazole usage beyond two years.
- The comparative study, which the sponsor has presented, pertains only to patients with Barrett's esophagus. This patient population is distinct and may manifest different responses to long-term omeprazole administration than the much larger group of patients who are being treated with this drug for GERD not necessarily associated with metaplastic changes of the esophagus.

As stated above, there are three areas of concern that have been raised by the Agency concerning the potential tumorogenic effects of omeprazole in patients. First, ECL cell hyperplasia that is associated with omeprazole-induced hypergastrinemia may progress to carcinoid tumors, or other G.I. tumors. Second, the genotoxic effects that have been observed by *in vitro* testing of omeprazole may be associated with carcinogenic effects in multiple tissues which are not necessarily confined to the gastrointestinal tract. Third, combined effects of omeprazole with comorbid conditions such as *H. Pylori* infection and atrophic gastritis may be linked to significant safety effects.

In a separate submission submitted in response to a request for information from the agency sent recently (see above) the sponsor has provided information on post-marketing safety surveillance of patients treated with the drug. Of concern is the accrual of 32 reports of gastric/duodenal carcinoids, 13 of which lacked evidence of conditions linked to gastrinoma or pernicious anemia. In addition, the sponsor has reported three cases of duodenal adenomatous polyps not linked to heredity polyposis syndromes, a relatively rare condition. From this experience it is clear that further tracking of mucosal neoplastic lesions in the post-marketing phase is crucial in order to exclude a causal link between neoplasia and omeprazole.

The delay in diagnosis of gastric malignancy attributable to omeprazole treatment in a small group of patients (4/49 reported cases). Analysis of the submitted narratives suggests that the delay was due to temporary alleviation of symptoms or endoscopic findings showing improvement of malignant lesions or synchronous nonmalignant lesions. In some cases, a diagnosis of malignancy was made 10 months or longer after the beginning of symptoms.

In extrapolating whether omeprazole-linked maligancy to an OTC population poses a significant risk, a number of important limitations must be addressed. These include:

- Limitations of detecting omeprazole-linked malignancy in a large population by volunteer reporting.

- The prediction that there is a long lag phase between drug exposure and malignancy.

- High background rates of certain GI malignancies (eg colorectal and pancreatic Ca) that would 'drown out' weak signals.

- Lack of prospective or nested cohort studies to track patients who have been treated with omeprazole over a long period of time.

- Lack of definition of groups that may be especially vunerable to the carcinogenic effects of omeprazole. Such subsets of consumers may be diluted by individuals who are not at increased risk for malignancy when exposed to the drug. The sponsor has provided information obtained from long-term clinical trials in which adult patients were treated with omeprazole between 2 and 14 years. Analysis of

results of these studies revealed that there is no evidence of progression of ECL cell hyperplasia to severe grades of ECL cell pathology. This experience is corroborated by the lack of a significant number of adverse case reports of carcinoid tumors in patients treated with omeprazole. Although very reassuring, the aforementioned data do not preclude the possibility that the susceptibility for ECL cellular transformation and tumor progression is different susceptible individuals. Such a difference(s) could occur as a result of developmentally modulated biological characteristics such as altered ratios of undifferentiated (precursor) cells in organs during the growth phase of development. In addition, after a putatively rare drug-induced perturbation of target cells, the emergence of carcinoid tumors probably requires other superimposed genetic 'hits'. This process is predicted to be time dependent and requires a long latency (years) until a malignant neoplasm would form. Analogously, in the case of sporadic colon cancer in adults, such time dependent accrual of multiple growth selective genetic 'hits' in target colonocytes is well characterized. Because of the short duration and the relatively small number of pediatric patients that were studied by the sponsor, it is not possible to exclude that in a large pediatric population treated with omeprazole (short-term and/or maintenance treatment), a time-linked association with carcinoid tumors will emerge. For this reason, the absence of a pattern of adverse reports of carcinoid tumors in patients treated with omeprazole does not preclude a long-term carcinogenic effect of the drug in some individuals. In addition, the absence of a comprehensive long-term follow-up of all members of defined study groups of patients taking omeprazole underscores the limitations of the world-wide voluntary side-effect reporting system (SafeTNet) that has been instituted by the sponsor. Because of sporadic/voluntary/ spontaneous reporting by only a small percentage of individuals treated with the drug, results of adverse side-effects may be misleading.

Rebound of Gastric Acid Secretion

Acid rebound is defined as an increase in gastric acid secretion (basal and/or stimulated) above pretreatment levels after discontinuation of anti-secretory therapy. Mechanisms associated with rebound include increases in serum gastrin concentrations and increased sensitivity to histamine (eg upregulation of H_2 receptors). Factors that lead to acid rebound following anti-secretory therapy are linked to the pharmacologically induced degree and duration of acid suppression. In addition, H. Pylori infection may augment acid rebound[15] . The sponsor has cited 9 clinical studies that measure the potential for acid rebound after discontinuation of omeprazole treatment (duration of treatment up to 3 months). These are summarized in Table 31.

[15] D Gillen et al. Rebound hypersecretion after omeprazole and its relation to on-treatment acid suppression and Helicobacter pylori status. Gastroenterology 1999; 116(2):239-247.

TABLE 31
Rebound - Studies with Omeprazole

REFERENCE	PATIENTS	TREATMENT, DAILY DOSE(S), DURATION	INTRAGASTRIC ACID MEASUREMENTS	BASELINE ACID SECRETION	TIME TO FOLLOW-UP MEASUREMENT AFTER TREATMENT DISCONTINUATION	POST-TREATMENT ACID SECRETION
Lind et al [5]	6 healthy patients	O 20, 40, 60, 80 mg (single dose)	P-stimulated acid secretion	Approx. 9 mmol/ 15 min	1, 3, 4, 14 days	No rebound hypersecretion
Sharma et al [6]	9 patients with duodenal ulcer	O 30-60 mg x 2 wks	24-hour acidity	Mean 24-hr acidity, 38.7 mmol/L	1 week, 8 wks	No rebound hypersecretion
Muller et al Z [7]	8 healthy patients	O 3C mg x 28c	Basal and P-stimulated acid output	Basal: mean, approx. 3 mmol/h; P-stimulated: mean, 27 mmol/h	1, 3, 5, 7, 1: days	No rebound hypersecretion
Prewett et al [8]	22 healthy patients	O 40 mg x 25 d R 300 mg x 25 d	Nocturnal intragastric acidity	Median 627 mmol-h/L	3, 6, 9, 12, 15, 18, 21 days	No rebound hypersecretion with O; rebound hypersecretion at 3, 6 days with R
Bell et al [9]	30 healthy patients with gastric acid hypersecretion	O 20 mg x 4 wk R 300 mg x 4 wk Placebo x 4 wk	24-hour acidity and plasma gastrin	Peak acid output > 26 mmol/hr	1, 7, 28 days	No rebound hypersecretion with O at days 1, 7, 28; rebound hypersecretion on day 1 with R

P: PENTAGASTRIN, O: OMEPRAZOLE, R: RANITIDINE, CSP: CISAPRIDE, NR: NOT REPORTED

TABLE 31 (continued)
Rebound - Studies with Omeprazole

REFERENCE	PATIENTS	TREATMENT, DAILY DOSE(S), DURATION	INTRAGASTRIC ACID MEASUREMENTS	BASELINE ACID SECRETION	TIME TO FOLLOW-UP MEASUREMENT AFTER TREATMENT DISCONTINUATION	POST-TREATMENT ACID SECRETION
Orr et al [10]	17 patients with heartburn	O 20 mg x 1 wk R 900 mg x 1 wk	24-hour esophageal pH monitoring	NR	1 or 3 days	No rebound hypersecretion
Waldum et al [11]	9 patients with reflux esophagitis	O 40 mg x 90 d	Basal and P-stimulated acid output	Basal: range, approx. 1-8 mmol/h P-stimulated: range, approx. 20-45 mmol/h	14 days	Rebound basal and stimulated hypersecretion
Gillen et al [12]	19 healthy patients	O 40 mg x 8 wks	Gastrin-17-stimulated acid output	Median, 34.2 and 36.0 mmol/h	6 days 16 days	Significantly increased acid output 6 and 16 days post-treatment
Fisher et al [13]	30 healthy patients	O 20 mg x 12 wks R 300 mg x 12 wks Cap 40 mg x 12 wks	Basal and P-stimulated acid output	NR	3 days and 1, 2, and 4 wks	Rebound hypersecretion with O and R 3 days post-treatment
Weinstein et al [14]	40 patients with Barrett's esophagus	O H-D ≤ 12 mos O H-D ≥ 24 mos R H-D ≥ 24 mos	P-stimulated acid output	NR	3 months	Rebound hypersecretion with O immediately but not 3 mos post-treatment

P: PENTAGASTRIN, O: OMEPRAZOLE, R: RANITIDINE, CSP: CISAPRIDE, NR: NOT REPORTED, H-D: HIGH-DOSE

The results of these studies are mixed. In many of the studies in which the treatment phase was two weeks or less acid rebound was not observed, after discontinuation of omeprazole. In contrast, in a study by Waldam et al, after a 90 day treatment period with omeprazole 40 mg daily, there was a significant rise in basal acid output in 3/8 patients, 14 days after discontinuation of omeprazole. This rise may be interpreted to reflect an increase in size and number of ECL cells, a consequence of the effects of longstanding anti-secretory treatment. Consistent with this interpretation was the observed increase in serum chromogranin A. Administration of omeprazole 40 mgs daily for eight weeks in healthy patients was linked to an increase of maximal acid output measured at 6 and 16

days post-treatment. This increase correlated with individual rises in serum gastrin concentrations during omeprazole treatment, suggesting that there is a trophic effect on parietal cells. In a study by Fischer et al,[16] both omeprazole 20 mg daily and ranitidine 150 mg bid (the recommended treatment dose for peptic ulcers which is double the labeled limit for OTC use) were associated with increases in basal acid secretion 3 days post-treatment. After long-term treatment with omeprazole, Weinstein et al[17] observed that patients with Barrett's esophagus developed a significant increase in pentagastrin stimulated acid secretion which returned to normal 3 months after cessation of therapy.

From a clinical perspective, despite the fact that most patients with GERD-related reflux esophagitis heal during treatment with omeprazole, there is a high recurrence rate, both of symptoms and inflammatory disease, within a short time after cessation of therapy. In one study, almost all patients with severe esophagitis healed during the treatment phase. Nonetheless, within 30 weeks of discontinuation of PPI therapy, more than 80% recurred. This finding is consistent with the concept that irrespective of the degree of inflammation, the underlying pathophysiological predisposition to develop esophagitis remains.

From these data the following can be concluded:

- Omeprazole associated acid rebound is reflected both by increases in basal and pentagastrin stimulated acid secretion. This effect is variable and may be linked to the extent of acid suppression as well as duration of treatment.
- Acid rebound occurs following treatment with H_2 receptor antagonists at doses which are recommended for the treatment of peptic ulcers.
- Acid rebound is self-limited after discontinuation of treatment with omeprazole.
- No information is available to determine whether acid rebound plays a role in patterns of self-medication by OTC subjects.
- H. Pylori may influence in variable ways the development of acid rebound after cessation of omeprazole treatment.
- Pronounced acid rebound in a subset of susceptible individuals in the population at large cannot be excluded especially after long-term omeprazole use. Such a phenomenon would not necessarily be detected in studies which enroll small numbers of test subjects.

Genotoxic Potential of Omeprazole

A cause for concern about the carcinogenic potential of omeprazole in humans is that based on the results of *in vitro* and *in vivo* testing, the agent and its S-enantiomer, H 199/18, which is a component of the formulation in Prilosec, may be genotoxic in a number of cell lineages, not limited to the GI tract. Although results of mutagenicity

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[16] RS Fisher et al. Rebound acid hypersecretion after gastric acid suppressant therapy. A short-lived (<1-week) phenomenon. Gastroenterology 1998; 114(4 Suppl Pt 2):A13.

[17] WM Weinstein et al. Acid hypersecretion parietal cell hyperplasia, and endoscopic changes after withdrawal of long term high dose omeprazole therapy: a prospective study. Gastroenterology 1996; 110(4 Suppl):A294.

testing using the Ames Salmonella typhimurium test have been consistently negative, both *in vivo* and *in vitro* exposure of mouse cells to the agent has been tied to clastogenic effects. Positive testing has been observed in a mouse bone marrow micronucleus assay and chromosome aberration has been noted in peripheral human lymphocytes exposed *in vivo* and *in vitro* to the agent, respectively. The question whether omeprazole is genotoxic in humans has been raised by a report of increased sister chromatid exchanges (SCEs) in peripheral lymphocytes obtained from subjects treated with omeprazole.[18] This finding has not been reported elsewhere in the medical literature. With regards to carcinogenesis in humans, the clinical significance of the limited range of positive testing of omeprazole has not been addressed. Furthermore, whether genotoxic effects of this agent on target cells that emanate from a variety of lineages has a greater impact on enhancing the risk for carcinogenicity in pediatric patients in comparison to adult patients is unknown.

There is a substantial body of information regarding the testing of omeprazole and its S-enantiomer H199/18 (which is a component of the racemic mixture contained in Prilosec) for genotoxicity. Results of these studies can be summarized as follows:

- Ames Salmonella typhirium, assay – Omeprazole and H 199/18 were not mutagenic in this assay.
- *In vitro* chromosomal aberration assay – In limited concentration ranges omeprazole and H 199/18 induced a significant number of chromosomal aberrations in human lymphocytes. In the case of omeprazole, a statistically significant increase was noted at a concentration of 345.4 mg/L when compared to the solvent alone control. H 199/18 was clastogenic at concentrations of 0.56 mM or higher.
- No significant increases in chromosomal aberrations were noted in mouse bone marrow cells after administration of omeprazole to CD-1 mice (110, 367 and 1,100 mg/kg) by oral gavage.
- H 199/18 was not clastogenic in two *in vivo* cytogenetic assays, a bone marrow micronucleus test and a rat bone marrow chromosome aberration test, even at toxic doses that caused deaths in some animals.

The genotoxic effects that have been observed in some *in vitro* tests of omeprazole may reflect carcinogenic properties of the systemically circulating agent on susceptible cells which need not be confirmed to the gastrointestinal tract. Susceptibility of cells to omeprazole or H 199/18 genotoxicity may be related not only to parameters of drug exposure alone, but also to growth related phases of target cells that are modulated during development. Third, although omeprazole may not be carcinogenic to gastric epithelium alone, a combined additive or synergistic effect, to form tumors, linked with the metaplastic and/or dysplastic associated changes that are known to be caused by *H. Pylori* infection in some patients must be ruled out.

The sponsor has provided information regarding *in vitro* and *in vivo* testing of omeprazole and H 199/18 for genotoxicity. Omeprazole is in a class of benzimidazole

[18] C. Thompson et al. *Comparative effects of omeprazole, cimetidine and ranitidine on sister chromatid exchange frequencies in lymphocytes of healthy human subjects.* Gastroenterology 102[4, part 2]: A177, 1991

proton pump inhibitors. In a milieu of a low pH these pro-drugs are converted to a highly unstable DNA-reactive sulfenimide metabolite. Extensive testing of omeprazole in rodents has revealed that it does not induce the formation of neoplasms other than carcinoid tumors in rats. Omeprazole and H 199/18 are not mutagenic in the Ames Salmonella typhirium assay. This reduces the likelihood that there is a *high* risk that these agents are hazardous in humans. In the face of inconsistently positive results yielded by the testing of omeprazole and H 199/18 in chromosomal aberration assays, it is not possible to exclude the possibility of genotoxicity in humans with an associated (possible *low*) risk of carcinogenicity. Therefore, the clinical relevance of the observation that omeprazole and H 199/18 are clastogenic *in vitro* is elusive. Even if these agents were carcinogenic in humans, with the information that is currently available and taking into account the limited predictive value of the assays that have been performed, it would not be possible to quantify a risk in patients being administered the drug, determine which organ systems would be vulnerable to tumor formation or assess a differential risk in certain patients (eg adolescents). Thus, a global assessment of the risk of carcinogenicity in susceptible patients cannot be determined by the battery of genotoxic testing that has been performed. Based on the information that the sponsor has provided it cannot be definitely determined that omeprazole does not have a carcinogenic potential in some individuals. However, its track record in adult patients until now suggests that the risk in the population as a whole may be low or negligible.

CONCLUSIONS

The sponsor is seeking approval for approval of omeprazole magnesium 20 mg for the treatment or prevention of occasional episodic heartburn. This condition is distinct from chronic heartburn linked to GERD. In assessing the safety profile of omeprazole for an OTC setting in the US it is important to determine whether both of these conditions will be treated. If individuals with GERD will comprise a significant element of the self-medicating population, because of the high recurrence rate of symptoms after cessation of anti-heartburn treatment, a high likelihood that some consumers will use the product either chronically or intermittently must be taken into account in a safety analysis. In addition, the development of an OTC indication of self-medication for individuals with GERD must take into account the need to avoid a substantial delay in diagnosis or pharmacological masking of significant complications that require timely recognition and care by a physician.

Occasional episodic heartburn is effectively managed by self-administration of agents which have a rapid onset and relatively short-lasting duration of action. The fact that maximal suppression of gastric acid secretion is only achieved after 2 or 3 days of daily treatment with omeprazole and that after each dose, there is a long duration of acid suppression suggests that this drug is very suitable for heartburn prevention rather than for the immediate relief of occasional episodic symptoms by the administration of a single tablet. Actual use studies were characterized by recruitment of many individuals who suffer from chronic heartburn symptoms consistent with GERD. The studies demonstrated that a large percentage of people who were self medicated with omeprazole

to prevent heartburn used the drug for more than 10 days continuously. This observation is consistent with the prediction that in addition to short-term users some consumers will use the drug, either chronically or intermittently.

An analysis of adverse events associated with short-term drug exposure (less than 12 weeks) has revealed that Omeprazole can be linked to the following:

- A range of liver toxicities in small percentage of patients. The toxicity is usually mild, idiosyncratic, self-limited and is reversed upon drug withdrawal. However, the drug causes significant hepatocellular necrosis in some individuals and has been linked to a few deaths. Although rare, causality of significant hepatocellular damage has been confirmed in some cases by dechallenge/rechallenge with omeprazole.
- Toxic Epidermal Necrolysis and Stevens-Johnson Syndrome. Although very rare, some cases have been linked to death
- Agranulocytosis and other disorders of marrow suppression. These are a rare events which usually, although not always, are reversible upon drug withdrawal
- Anaphylaxis/Angioedema. In some cases of immediate hypersensitivity with symptoms of urticaria, wheezing, rash, swelling, etc clear causality with omeprazole has been proven by successful dechallenge and rechallenge with the drug. The incidence of hypersensitivity responses is high enough to have been detected in clinical trials and be as high as 0.5 per 1000 users of omeprazole

Special Populations in Which OTC Omeprazole Has Been Linked to Important Concerns

- Pediatric subjects. Currently, omeprazole is not approved for prescription use in adolescents. The numbers of clinical study subjects in this age group and the numbers of AEs reported in the post-marketing database are too small to determine whether adolescents have differential susceptibilities to develop rare toxic events linked to omperazole.
- Pregnancy. Currently, Omeprazole is categorized as a 'Class C' drug because of fetal toxicity in an animal model. On the other hand, off-label use in humans has not demonstrated omeprazole-linked loss of fertility or teratogenicity.
- Drug-drug interactions. In conjunction to affects on absorption of anti-fungal drugs omeprazole has the potential to reduce clearance of drugs that are metabolized by CYP2C19 such as diazepam, phenytoin, R-warfarin and tolbutamide. In the case of diazepam, an omeprazole-induced reduction of 25% may be clinically significant in individuals who are particularly susceptible, such as those with liver disease.

An analysis of adverse events associated with long-term drug exposure (more than 12 weeks) has revealed that Omeprazole can be linked to the following:

- Masking of disease.
- Prolonged hypergastrinemia and Genotoxic Potential of Omeprazole. Hypergastrinemic responses to omeprazole may be more pronounced in some people

such as those with H. Pylori infection or 'slow metabolizers'. Although in the general undifferentiated population of the US there is no clear tumor association with omeprazole, the possibility of that there are oncogenic effects in susceptible groups who are exposed to omeprazole for very long periods of time has not been ruled out.

- Rebound of Acid Secretion.

RECOMMENDATIONS FOR REGULATORY ACTION

1. Adequate labeling that warns consumers about rare side-effects related to short-term exposure to omeprazole is necessary. The warnings should give information required for early recognition and instruct patients to seek attention by a physician. Rare side effects that should be listed include liver toxicity, bone marrow suppression, skin toxicity and hypersensitivity reaction.

2. The lower age limit for OTC use of omeprazole should be 18.

3. The sponsor should develop registries to study the outcome of pregnancy in users of omeprazole. In addition, omeprazole must pass muster for a Category 'B' status to justify its approval for OTC use.

4. Because of the absence of a learned intermediary, labeling should indicate the possibility of drug-drug interactions to protect individuals treated with multiple drugs who may develop drug toxicity due to exaggerated drug-drug interactions.

5. Adequate consideration by an Advisory Committee that is comprised of consumer advocates, family practitioners and specialists should be given to establish whether benchmarks for safe and effective use of PPIs in an OTC setting for the treatment of GERD can be set. Subsequently, it should be determined whether GERD/ chronic heartburn can be treated safely and effectively in an OTC setting with omeprazole, if endoscopy has not been performed. The sponsor should be asked to provide studies which demonstrate that treatment of chronic heartburn with omeprazole-Mg is effective and Actual Use Studies which demonstrate that there is adequate adherence to appropriately modified labeling. To ensure that individuals with GERD will be triaged appropriately, labeling that lists 'alert' and atypical symptoms requiring immediate physician evaluation should be considered.

6. Phase IV studies to investigate the incidence of GI adenocarcinomas and other malignancies using long-term prospective or nested case control study designs in large numbers of omeprazole exposed individuals should be performed by the sponsor.

7. To adjudicate whether the acid rebound phenomenon associated with cessation of omeprazole treatment is clinically meaningful, studies to determine AEs at the time

of cessation of treatment and the rate of reinstitution of acid suppression therapy (within 1 month after completion of a course of treatment) should be provided by sponsor.

8. At this time approval of omeprazole-Mg for OTC use should be denied.

/S/

Mark Avigan, M.D., C.M.

cc:
NDA 21-229
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/MAvigan
HFD-181/MWalsh
HFD-180/JChoudary
HFD-180/LZhou
r/d 11/7/00 jgw
f/t
N/21229010.1MA

APPEARS THIS WAY
ON ORIGINAL

APPENDIX 1

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

Adverse Events for Ome-Mg[a] and Placebo OTC Subjects[b]
Summary by Body System, COSTART Term and Treatment Group

Body System/COSTART Term	Ome-Mg (n=8179)[c]		Placebo (n=3120)[c]		Overall (n=11299)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
Body as a Whole						
ABCESS	1	<1%[f]	0	0%	1	<1%[f]
ALLERG REACT	4	<1%[f]	4	<1%[f]	8	<1%[f]
ASTHENIA	6	<1%[f]	4	<1%[f]	10	<1%[f]
CARCINOMA	1	<1%[f]	0	0%	1	<1%[f]
CELLULITIS	1	<1%[f]	0	0%	1	<1%[f]
CHILLS	1	<1%[f]	0	0%	1	<1%[f]
CYST	0	0%	1	<1%[f]	1	<1%[f]
DEATH	1	<1%[f]	0	0%	1	<1%[f]
EDEMA FACE	2	<1%[f]	0	0%	2	<1%[f]
FEVER	14	<1%[f]	3	<1%[f]	17	<1%[f]
FLU SYND	63	1%	13	<1%[f]	76	1%
HANGOVER	1	<1%[f]	0	0%	1	<1%[f]
HEADACHE	439	5%	109	3%	548	5%
HERNIA	2	<1%[f]	0	0%	2	<1%[f]
INFECT	24	<1%[f]	12	<1%[f]	36	<1%[f]
INFECT FUNG	2	<1%[f]	3	<1%[f]	5	<1%[f]
INFECT VIRAL	2	<1%[f]	0	0%	2	<1%[f]
INJURY ACCID	21	<1%[f]	3	<1%[f]	24	<1%[g]
MALAISE	7	<1%[f]	2	<1%[f]	9	<1%[f]
NECK RIGID	4	<1%[f]	2	<1%[f]	6	<1%[f]
PAIN	48	1%	6	<1%[f]	54	<1%[f]
PAIN ABDO	46	1%	8	<1%[f]	54	<1%[f]
PAIN BACK	70	1%	16	1%	86	1%
PAIN CHEST	18	<1%[f]	5	<1%[f]	23	<1%[f]
PAIN NECK	12	<1%[f]	1	<1%[f]	13	<1%[f]
PAIN PELVIC	1	<1%[f]	1	<1%[f]	2	<1%[f]
PHOTOSENSITIVITY	1	<1%[f]	0	0%	1	<1%[f]
REACT AGGRAV	1	<1%[f]	0	0%	1	<1%[f]
REACT UNEVAL	1	<1%[f]	0	0%	1	<1%[f]
Overall	692	8%	178	6%	870	8%
Cardiovascular System						
ANGINA PECTORIS	2	<1%[f]	0	0%	2	<1%[f]
ARRHYTHMIA	1	<1%[f]	1	<1%[f]	2	<1%[f]
ARTERIOSCLEROSIS	1	<1%[f]	0	0%	1	<1%[f]
CARDUINEGAKT	1	<1%[f]	9	0%	1	<1%[f]
CARDIOMYOPATHY	0	0%	1	<1%[f]	1	<1%[f]
FIBRILLATATR	1	<1%[f]	1	<1%[f]	2	<1%[f]
HEART FAIL RIGHT	0	0%	1	<1%[f]	1	<1%[f]
HYPERTENS	5	<1%[f]	4	<1%[f]	9	<1%[f]
INFARCT MYOCARD	1	<1%[f]	0	0%	1	<1%[f]
MIGRAINE	11	<1%[f]	3	<1%[f]	14	<1%[f]
PALPITAT	3	<1%[f]	1	<1%[f]	4	<1%f
SYNCOPE	1	<1%[f]	0	0%	1	<1%[f]
TACHYCARDIA	5	<1%[f]	1	<1%[f]	6	<1%[f]
THROMBOPHLEB	1	<1%[f]	0	0%	1	<1%[f]
VASODILAT	5	<1%[f]	1	<1%[f]	6	<1%[f]
Overall	37	<1%[f]	12	<1%[f]	49	<1%[f]
Digestive System						
ABSCESS PERIODONT	4	<1%[f]	3	<1%[f]	7	<1%[f]
ANOREXIA	3	<1%[f]	3	<1%[f]	6	<1%[f]

	Omg-Mg (n=8179)[c]		Placebo (n=3120)[c]		Overall (n=11299)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
APPETITE INC	2	<1%[f]	1	<1%[f]	3	<1%[f]
COLITIS	3	<1%[f]	0	0%	3	<1%[f]
CONSTIP	40	<1%[f]	9	<1%[f]	49	<1%[f]
DIARRHEA	167	2%	56	2%	223	2%
DRY MOUTH	21	<1%[f]	4	<1%[f]	25	<1%[f]
DYSPEPSIA	54	1%	9	<1%[f]	63	1%
ERUCTAT	9	<1%[f]	0	0%	9	<1%[f]
ESOPHAGITIS	0	0%	1	<1%[f]	1	<1%[f]
FLATUL	88	1%	14	<1%[f]	102	1%
GASTRITIS	2	<1%[f]	1	<1%[f]	3	<1%[f]
GASTROENTERITIS	7	<1%[f]	6	<1%[f]	13	<1%[f]
GI DIS	4	<1%[f]	1	<1%[f]	5	<1%[f]
HEM GI	1	<1%[f]	1	<1%[f]	2	<1%[f]
HEPATITIS C	0	0%	1	<1%[f]	1	<1%[f]
HERPES SIMPLEX	2	<1%[f]	4	<1%[f]	6	<1%[f]
LIVER FUNC ABNORM	11	<1%[f]	1	<1%[f]	12	<1%[f]
NAUSEA	112	1%	30	1%	142	1%
PAIN	23	<1%[f]	4	<1%[f]	27	<1%[f]
PAIN ABDO	70	1%	22	1%	92	1%
RECTAL DIS	1	<1%[f]	0	0%	1	<1%[f]
SALIV GLAND ENLARGE	1	<1%[f]	0	0%	1	<1%[f]
SIALADENITIS	1	<1%[f]	0	0%	1	<1%[f]
STOMATITIS	2	<1%[f]	0	0%	2	<1%[f]
STOMATITIS APHTH	1	<1%[f]	0	0%	1	<1%[f]
STOMATITIS ULCER	1	<1%[f]	0	0%	1	<1%[f]
STOOL ABNORM	2	<1%[f]	0	0%	2	<1%[f]
THRIST	1	<1%[f]	0	0%	1	<1%[f]
TONGUE DIS	2	<1%[f]	1	<1%[f]	3	<1%[f]
TOOTH DIS	5	<1%[f]	3	<1%[f]	8	<1%[f]
ULCER MOUTH	0	0%	3	<1%[f]	3	<1%[f]
ULCER STOMACH	0	0%	1	<1%[f]	1	<1%[f]
VOMIT	45	1%	18	1%	63	1%
Overall	555	7%	154	5%	709	6%
Endocrine System						
DIABETES MELL	1	<1%[f]	0	0%	1	<1%[f]
HYPOTHYR	1	<1%[f]	0	0%	1	<1%[f]
Overall	2	<1%[f]	0	0%	2	<1%[f]
Hemic and Lymphatic						
ANEMIA	2	<1%[f]	0	0%	2	<1%[f]
ANEMIA HYPOCHROM	4	<1%[f]	0	0%	4	<1%[f]
ECCHYMOSIS	7	<1%[f]	1	<1%[f]	8	<1%[f]
LYMPHADENO	1	<1%[f]	0	0%	1	<1%[f]
Overall	14	<1%[f]	1	<1%[f]	15	<1%[f]
Metabolic and Nutritional Disorders						
CREATININE INC	2	<1%[f]1	1	<1%[f]	3	<1%[f]
EDEMA	3	<1%[f]	0	0%	3	<1%[f]
EDEMA GENERAL	2	<1%[f]	0	0%	2	<1%[f]
EDEMA PERIPH	9	<1%[f]	2	<1%[f]	11	<1%[f]
GOUT	2	<1%[f]	0	0%	2	<1%[f]
HYPERCHOLESTEREM	0	0%	2	<1%[f]	2	<1%[f]
HYPERGLYCEM	1	<1%[f]	0	0%	1	<1%[f]
SGOT INC	6	<1%[f]	1	<1%[f]	7	<1%[f]
SGPT INC	7	<1%[f]	1	<1%[f]	8	<1%[f]
Overall	28	<1%[f]	7	<1%[f]	35	<1%[f]
Musculo-Skeletal System						
ARTHRALGIA	29	<1%[f]	8	<1%[f]	37	<1%[f]

	Ome-Mg (n=8179)[c]		Placebo (n=3120)[c]		Overall (n=11299)[c]	
	n[d]	%[e]	nd	%[e]	n[d]	%[e]
ARTHRITIS	5	<1%[f]	2	<1%[f]	7	<1%[f]
ARTHROSIS	0	0%	1	<1%[f]	1	<1%[f]
BONE FRACT SPONTAN	1	<1%[f]	0	0%	1	<1%[f]
BURSITIS	1	<1%[f]	0	0%	1	<1%[f]
CRAMPS LEG	5	<1%[f]	2	<1%[f]	7	<1%[f]
FIBRO TENDON	1	<1%[f]	0	0%	1	<1%[f]
INJURY ACCID	0	0%	1	<1%[f]	1	<1%[f]
JOINT DIS	7	<1%[f]	5	<1%[f]	12	<1%[f]
MYALGIA	31	<1%[f]	11	<1%[f]	42	<1%[f]
MYOPATHY	1	<1%[f]	0	0%	1	<1%[f]
PAIN BONE	1	<1%[f]	0	0%	1	<1%[f]
TENDON DIS	2	<1%[f]	2	<1%[f]	4	<1%[f]
Overall	83	1%	31	1%	114	1%
Nervous System						
AGITATION	1	<1%[f]	0	0%	1	<1%[f]
ANXIETY	8	<1%[f]	4	<1%[f]	12	<1%[f]
CONFUS	1	<1%[f]	1	<1%[f]	2	<1%[f]
DELUSIONS	1	<1%[f]	0	0%	1	<1%[f]
DEPRESSION	1	<1%[f]	4	<1%[f]	5	<1%[f]
DIZZINESS	42	1%	8	<1%[f]	50	<1%[f]
EMOTION LABIL	0	0%	1	<1%[f]	1	<1%[f]
HYPERTONIA	3	<1%[f]	0	0%	3	<1%[f]
HYPESTHESIA	2	<1%[f]	0	0%	2	<1%[f]
INSOMNIA	18	<1%[f]	6	<1%[f]	24	<1%[f]
MENINGITIS	1	<1%[f]	0	0%	1	<1%[f]
NERVOUSNESS	7	<1%[f]	2	<1%[f]	9	<1%[f]
NEURALGIA	1	<1%[f]	0	0%	1	<1%[f]
NEUROPATHY	1	<1%[f]	3	<1%[f]	4	<1%[f]
PARESTHESIA	3	<1%[f]	3	<1%[f]	6	<1%[f]
SLEEP DIS	2	<1%[f]	0	0%	2	<1%[f]
SOMNOLENCE	8	<1%[f]	4	<1%[f]	12	<1%[f]
SPEECH DIS	1	<1%[f]	0	0%	1	<1%[f]
THINKING ABNORM	0	0%	1	<1%[f]	1	<1%[f]
TREMOR	1	<1%[f]	0	0%	1	<1%[f]
VERTIGO	3	<1%[f]	0	0%	3	<1%[f]
Overall	96	1%	33	1%	129	1%
Respiratory System						
ASTHMA	7	<1%[f]	3	<1%[f]	10	<1%[f]
BRONCHIECTASIS	1	<1%[f]	0	0%	1	<1%[f]
BRONCHITIS	22	<1%[f]	5	<1%[f]	27	<1%[f]
COUGH INC	31	<1%[f]	7	<1%[f]	38	<1%[f]
DYSPNEA	9	<1%[f]	3	<1%[f]	12	<1%[f]
EDEMA LARYNX	1	<1%[f]	0	0%	1	<1%[f]
EPISTAXIS	5	<1%[f]	3	<1%[f]	8	<1%[f]
HICCUP	1	<1%[f]	1	<1%[f]	2	<1%[f]
INFECT	167	2%	50	2%	217	2%
LARYNGITIS	0	0%	1	<1%[f]	1	<1%[f]
LUNG DIS	2	<1%[f]	2	<1%[f]	4	<1%[f]
PHARYNGITIS	49	1%	12	<1%[f]	61	1%
PLEURAL DIS	0	0%	1	<1%[f]	1	<1%[f]
PNEUMONIA	5	<1%[f]	0	0%	5	<1%[f]
RESPIRAT DIS	1	<1%[f]	0	0%	1	<1%[f]
RHINITIS	40	<1%[f]	14	<1%[f]	54	<1%[f]
SINUSITIS	40	<1%[f]	12	<1%[f]	52	<1%[f]
VOICE ALTERAT	2	<1%[f]	0	0%	2	<1%[f]
Overall	326	4%	107	3%	433	4%

	Ome-Mg (n=8179)[c]		Placebo (n=3120)[c]		Overall (n=11299)[c]	
Skin and Appendages						
ACNE	3	<1%[f]	1	<1%[f]	4	<1%[f]
ALOPECIA	0	0%	1	<1%[f]	1	<1%[f]
ANGIOEDEMA	1	<1%[f]	0	0%	1	<1%[f]
APPLICAT SITE REACT	5	<1%[f]	0	0%	5	<1%[f]
CARCINOMA SKIN	1	<1%[f]	0	0%	1	<1%[f]
DERM CONTACT	1	<1%[f]	0	0%	1	<1%[f]
FURUNCULOSIS	1	<1%[f]	0	0%	1	<1%[f]
PAIN	1	<1%[f]	0	0%	1	<1%[f]
PRURITUS	9	<1%[f]	2	<1%[f]	11	<1%[f]
PSORIASIS	1	<1%[f]	0	0%	1	<1%[f]
RASH	21	<1%[f]	7	<1%[f]	28	<1%[f]
SKIN DIS	11	<1%[f]	2	<1%[f]	13	<1%[f]
SKIN DRY	1	<1%[f]	0	0%	1	<1%[f]
SWEAT	0	0%	1	<1%[f]	1	<1%[f]
URTICARIA	4	<1%[f]	1	<1%[f]	5	<1%[f]
Overall	57	1%	15	<1%[f]	72	1%
Special Senses						
AMBLYOPIA	1	<1%[f]	1	<1%[f]	2	<1%[f]
CONJUNCTIVITIS	3	<1%[f]	4	<1%[f]	7	<1%[f]
DIPLOPIA	1	<1%[f]	0	0%	1	<1%[f]
DRY EYE	0	0%	1	<1%[f]	1	<1%[f]
EAR DIS	1	<1%[f]	3	<1%[f]	4	<1%[f]
EYE DIS	3	<1%[f]	0	0%	3	<1%[f]
GLAUCOMA	1	<1%[f]	0	0%	1	<1%[f]
HEM EYE	1	<1%[f]	0	0%	1	<1%[f]
INJURY ACCIDENTAL	1	<1%[f]	0	0%	1	<1%[f]
OTITIS MED	2	<1%[f]	1	<1%[f]	3	<1%[f]
PAIN EAR	4	<1%[f]	1	<1%[f]	5	<1%[f]
PAIN EYE	2	<1%[f]	0	0%	2	<1%[f]
TASTE PERVERS	7	<1%[f]	1	<1%[f]	8	<1%[f]
TINNITUS	1	<1%[f]	1	<1%[f]	2	<1%[f]
VISION ABNORM	1	<1%[f]	0	0%	1	<1%[f]
Overall	28	<1%[f]	13	<1%[f]	41	<1%[f]
Urogenital						
AMENORRHEA	1	<1%[f]	0	0%	1	<1%[f]
ANURIA	1	<1%[f]	0	0%	1	<1%[f]
CARCINOMA CERVIX	0	0%	1	<1%[f]	1	<1%[f]
CYST	1	<1%[f]	0	0%	1	<1%[f]
CYSTITIS	1	<1%[f]	1	<1%[f]	2	<1%[f]
DYSMENORRHEA	14	<1%[f]	4	<1%[f]	18	<1%[f]
DYSURIA	3	<1%[f]	0	0%	3	<1%[f]
EPIDIDYMITIS	0	0%	1	<1%[f]	1	<1%[f]
HEM VAGINAL	1	<1%[f]	0	0%	1	<1%[f]
HEMATURIA	2	<1%[f]	0	0%	2	<1%[f]
INFECT URIN TRACT	12	<1%[f]	5	<1%[f]	17	<1%[f]
KIDNEY CALCULUS	3	<1%[f]	0	0%	3	<1%[f]
LACTATION FEM	1	<1%[f]	0	0%	1	<1%[f]
MASTITIS	2	<1%[f]	0	0%	2	<1%[f]
MENS DIS	1	<1%[f]	2	<1%[f]	3	<1%[f]
OLIGURIA	1	<1%[f]	0	0%	1	<1%[f]
PAIN BREAST	1	<1%[f]	0	0%	1	<1%[f]
PREGN UNINTEND	1	<1%[f]	1	<1%[f]	2	<1%[f]
PROSTAT DIS	3	<1%[f]	0	0%	3	<1%[f]
PYELONEPHRITIS	1	<1%[f]	0	0%	1	<1%[f]
URIN FREQUENCY	1	<1%[f]	1	<1%[f]	2	<1%[f]

	Ome-Mg (n=8179)[c]		Placebo (n=3120)[c]		Overall (n=11299)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
VAGINITIS	0	0%	2	<1%[f]	2	<1%[f]
Overall	48	1%	18	1%	66	1%

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.
[b] Includes subjects from the following studies: P&G 1997092, 1997095, 1998003, 1998005, 1998006, 1998014, 1998067; AMI 171, 183, 200 (only includes data from periods where tablet formulation was taken).
[c] Number of subjects evaluable for safety.
[d] Number of subjects who reported adverse events within specified Treatment Group, Body System, and COSTART Term:
[e] Percent of subjects who reported adverse events within specified Treatment Group, Body System, and COSTART Term: (n/N)*100
[f] Percentage <0.5% are reported as <1%.

TABLE 2

Integrated Summary of Safety - Prescription Capsule Clinical Trial Adverse Events
Table of Clinical Trials Included in Rx Omeprazole Safety Summary

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Astra Trial 1-603 Multicenter Belgium	TRIAL DESIGN: Double-blind, randomized, parallel group trial in patients with reflux esophagitis OBJECTIVE: To compare the rate of macroscopic healing of esophagitis after treatment with omeprazole and ranitidine	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: 1. Omeprazole 40 mg od 2. Ranitidine 150 mg bid Total	 31 30 61	 16-79 24-79 24-79
Astra Trial 1-605A Multicenter Denmark	TRIAL DESIGN: Double-blind, randomized, parallel group trial in patients with endoscopically proved reflux esophagitis OBJECTIVE: To compare the proportion of patients with macroscopic healing of esophagitis after treatment with omeprazole and ranitidine	TRIAL DURATION: 9 months total Daily dose week 1-12: 1 Omeprazole 40 mg od 2. Ranitidine 150 mg bid Followed by an additional 6 months follow-up without treatment Total	 82 84 166	 24-79 22-79 22-79
Astra Trial 1-606 Multicenter Austria, Germany, Switzerland	STUDY DESIGN: Double-blind, randomized, parallel group study in patients with erosive/ulcerative esophagitis OBJECTIVE: To document the effect on healing after treatment with omeprazole and ranitidine	STUDY DURATION: 4 weeks Daily dose week 1-4: 1. Omeprazole 20 mg od 2. Ranitidine 150 mg bid Total	 88 89 177	 19-79 20-78 19-79
Astra Trial 1-608A Multicenter Norway, Sweden	TRIAL DESIGN: Double-blind, randomized, parallel group trial in patientws with erosive/ulcerative esophagitis OBJECTIVE: To study the effect of treatment with omeprazole and ranitidine on macroscopic heling and symptoms	TRIAL DURATION: 14 months total Daily dose week 1-8: 1. Omeprazole 20 mg od 2. Ranitidine 150 mg bid Followed by an additional 12 months follow-up without treatment Total	 75 77 152	 19-80 19-80 19-80
Astra Trial 1-609A Multicenter Australia	TRIAL DESIGN: Double-blind, randomized trial with three parallel groups in patients with erosive peptic esophagitis. OBJECTIVE: To study the effect of treatment with omeprazole and placebo on macroscopic healing and symptoms	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: 1. Omeprazole 20 mg od 2. Omeprazole 40 mg od 3. Placebo Total	 16 16 32 64	 28-72 28-78 18-80 18-80
Astra Trial 1-609B Multicenter Australia	TRIAL DESIGN: Double-blind, randomized, parallel group trial in patients with erosive/ulcerative esophagitis OBJECTIVE: To trial the effect of treatment with two omeprazole regimens on macroscopic healing and symptoms	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: 1. Omeprazole 20 mg od 2. Omeprazole 40 mg od Total	 51 47 98	 24-78 19-84 19-84

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Astra Trial 1-613A. B Multicenter Norway, Sweden	TRIAL DESIGN: Double-blind, randomized, parallel group trial in patients with erosive esophagitis not responding to treatment with H2 receptor antagonists OBJECTIVE: To document the effect on healing in patients with erosive peptic esophagitis to treatment with omeprazole and ranitidine. During a 6 months follow-up period document if maintenance treatment with omeprazole and ranitidine prevents recurrence of esophagitis after healing	TRIAL DURATION: 9 months total Daily dose week 1-12: 1. Omeprazole 40 mg od 2. Ranitidine 300 mg bid Followed by an additional 6 months of omeprazole 20 mg od (Group 1) or ranitidine 150 mg bid (Group 2) Total	 51 47 98	 18-84 26-81 18-84
Astra Trial I-619 Multicenter Belgium, France	TRIAL DESIGN: Double-blind, randomized, parallel group trial in , patients with erosive/ulcerative esophagitis OBJECTIVE: To document the effect on healing in patients treated with omeprazole and ranitidine	TRIAL DURATION: 4-8 weeks Daily dose week 1-8: 1. Omeprazole 20 mg od 2. Ranitidine 150 mg bid Total	 76 80 156	 23-85 20-84 20-85
Astra Trial 1-621A, B Multicenter Australia	TRIAL DESIGN: Consisting of two parts, an initial healing phase and a maintenance treatment phase, in patients with erosive peptic esophagitis. The first part was open and the second part was a double-blind, randomized trial with three parallel groups. OBJECTIVE: The first part: to investigate the effect of treatment on objective indices of disease severity. The second part: to determine the recurrence rate following healing with two omeprazole regimens and ranitidine	TRIAL DURATION: 14 months total Daily dose week 1-8: Omeprazole 20 mg od Followed by an additional 12 months maintenance period with daily dose: 1. Omeprazole 20 mg od 2. Omeprazole 20 mg od as weekend therapy (20 mg od/20 mg od over 3 consecutive days) 3. Ranitidine 150 mg bid Total	 204 52 55 51 204	 21-80 21-76 26-80 31-77 21-80
Astra Trial 1-627A, B Multicenter Belgium, France	TRIAL DESIGN: Consisting of two parts, an initial healing phase and a maintenance treatment phase in patients with erosive/ulcerative esophagitis. The first part was open and the second part was a ddouble-blind, randomized, parallel group trial OBJECTIVE: The first part: to heal the patients. The second part: to document the effect of two omeprazole regimens on preventing the occurrence on symptoms and esophagitis	TRIAL DURATION: 8 months total Daily dose week 1-8: Omeprazole 20 mg od Followed by an additional 6 month maintenance period with daily dose: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od as weekend therapy (20 mg od/20 mg od/20 mg od over 3 consecutive days) Total	 108 44 42 108	 18-86 29-78 18-86 18-86

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Astra Trial 1-604A, B, C, D One center Denmark	TRIAL DESIGN: Consisting of two parts, an initial healing phase (A) and a maintenance phase (B, C, D), in patients with reflux esophagitis. The first part was a double-blind, randomized, parallel group trial. The second part was a doduble-blind, randomized trial with three parallel groups. Patients who relapsed from the maintenance phase entered an open re-healing treatment period and continued on open maintenance treatment. OBJECTIVE: The first part (A): to heal the patients with two omeprazole dosages. The second part (B, C, D): to determine the recurrence rates of esophagitis during a 6 months maintenance treatment period with two omeprazole dosages and placebo	TRIAL DURATION: 9 months total Daily dose week 1-12: 1. Omeprazole 20 mg od 2. Omeprazole 40 mg od Followed by an additional 6 months maintenance period with daily dose: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Patients who relapsed from the maintenance phase entered an open re-healing period for 12 weeks with daily dose: Omeprazole 40 mg od Healed patients continued on open maintenance treatment for 6 months with daily dose: Omeprazole 20 mg od Total	 110 110 68 67 33 79 72 220	 19-88 21-87 19-83 22-83 21-82 19-82 19-82 19-88
Astra Trial 1-641A, B, C Multicenter Scandinavia	TRIAL DESIGN: Consisting of two parts, an initial healing phase and a maintenance phase, in patients with erosive/ulcerative esophagitis. The first part was during the first 3 days double-blind and randomized with parallel groups, followed by open treatment. The second part was a double-blind, randomized trial with three parallel groups. Patients who relapsed from the maintenance phase continued on open maintenance treatment. OBJECTIVE: The first part: to compare the effect on reflux symptoms during the first 2 weeks of treatment with two omeprazole dosages. The second part: to, with two omeprazole dosages and ranitidine, document the rate of recurrence of the disease following healing.	TRIAL DURATION: 15 months total Daily dose day 1-3: 1. Omeprazole 20 mg od 2. Omeprazole 40 mg od Open daily dose day 4-12 weeks: Omeprazole 20/40 mg od Followed by an additional 12 months maintenance period with daily dose: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Ranitidine 150 mg bid Patients who relapsed from the maintenance phase entered open maintenance treatment for the remainder of the maintenance period with daily dose: Omeprazole 20 mg od Total	 215 211 426 133 131 128 105 426	 19-79 18-79 18-79 19-77 22-79 18-79 19-77 18-79

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Astra Trial 1-1601A, B Multicenter Denmark, Sweden	TRIAL DESIGN: Consisting of two parts, an initial phase and an on demand phase, in patients with gastroesophageal reflux symptoms without macroscopic esophagitis. The first part was a double-blind, randomized trial with three parallel groups. Patients still symptomatic after 4 weeks were treated on an open basis. The second part was a double-blind, randomized trial with three parallel groups. OBJECTIVE: The first part: to compare the efficacy of two omeprazole dosages and placebo on the relief of heartburn in the treatment of patients with heartburn as the predominant reflux symptom. The second part: to compare the efficacy of on demand treatment with two omeprazole dosages and placebo in patients with previously treated symptomatic gastroesophageal reflux disease	TRIAL DURATION: 8 months total Daily dose week 1-4: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Open daily dose week 5-8: Omeprazole 20 mg od Followed by an additional 6 months on demand treatment period with daily dose: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Total	 199 205 105 239 139 136 141 509	 20-81 20-79 19-78 20-79 20-81 19-79 20-79 19-81
Astra Trial 1-1602A. B Multicenter United Kingdom	TRIAL DESIGN: Consisting of two parts, an initial phase and a follow-up phase, in patients suffering from heartburn as the predominant symptom of gastroesophageal reflux disease. The first part was double-blind and randomized with three parallel groups. Patients still symptomatic after 4 weeks were treated on an open basis. The second part was a double-blind, randomized, parallel group trial. OBJECTIVE: The first part: to compare the efficacy of two omeprazole dosages and ranitidine on the relief of heartburn in the treatment of patients with heartburn as the predominant symptom of gastroesophageal reflux disease. The second part: to compare the efficacy and safety of continuous treatment with omeprazole and placebo following initial symptom relief.	TRIAL DURATION: 8 months total Daily dose week 1-4: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Ranitidine 150 mg bid Open daily dose week 5-8: Omeprazole 20 mg od Followed by an additional 6 months continuous treatment period with daily dose: 1. Omeprazole 10 mg od 2. Placebo Total	 338 328 326 438 242 253 992	 18-83 19-80 20-81 18-83 18-79 19-79 18-83

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Astra Trial 1-1603 Multicenter Multinational	TRIAL DESIGN: Double-blind, randomized trial with three parallel groups in patients complaining of upper gastro-intestinal discomfort. Patients still symptomatic after 4 weeks were treated on an open basis. OBJECTIVE: To compare the efficacy of two omeprazole dosages and placebo in respect of the relief of overall upper gastro-intestinal symptoms.	TRIAL DURATION: 8 weeks Daily dose week 1-4: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Open daily dose week 5-8: Omeprazole 20 mg od Total	 224 224 86 337 534	 18-79 18-80 20-79 18-79 18-80
Astra Trial SH-OMD-0001 Multicenter Germany	TRIAL DESIGN: Double-blind, randomized trial with four parallel groups in patients with severe and chronic dyspepsia OBJECTIVE: To compare two dosages of omeprazole, ranitidine and placebo with respect to symptomatic response rates after treatment.	TRIAL DURATION: 2 weeks Daily dose week 1-2: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Ranitidine 150 mg daily 4. Placebo Total	 202 193 193 201 789	 17-81 17-81 18-79 16-77 16-81
Astra Trial SH-OMD-0003 Multicenter Denmark, Sweden	TRIAL DESIGN: Double-blind, randomized, parallel group trial in patients with functional dyspepsia OBJECTIVE: To compare omeprazole and placebo regarding the proportion of patients with complete symptom relief of upper abdominal pain/discomfort	TRIAL DURATION: 2 weeks Daily dose week 1-2: 1. Omeprazole 20 mg bid 2. Placebo Total	 100 97 197	 18-71 18-66 18-71
Astra Trial SH-OMD-0007 Multicenter Multinational	TRIAL DESIGN: Double-blind, randomized trial with three parallel groups in patients with functional dyspepsia OBJECTIVE: To compare two omeprazole dosages and placebo regarding the proportion of patients with complete symptom relief of epigastric pain/discomfort	TRIAL DURATION: 4 weeks Daily dose week 1-4: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Total	 201 217 218 636	 19-78 18-75 18-77 18-78
Astra Trial SH-OMD-0008 Multicenter Multinational	TRIAL DESIGN: Double-blind, randomized trial with three parallel groups in patients with functional dyspepsia. OBJECTIVE: To compare two omeprazole dosages and placebo regarding the proportion of patients with complete symptom relief of epigastric pain/discomfort	TRIAL DURATION: 4 weeks Daily dose week 1-4: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Total	 200 203 204 607	 19-77 19-80 18-77 18-80

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Astra Merck Trial #037 Multicenter US	TRIAL DESIGN: Double-blind, randomized trial with three parallel groups in patients with moderate to severe heartburn associated with GERD. OBJECTIVE: To demonstrate that omeprazole safely and effectively resolves heartburn in patients with pathologic GERD but with no erosive esophagitis on endoscopy.	TRIAL DURATION: 4 weeks Daily dose week 1-4: 1. Omeprazole 10 mg od 2. Omeprazole 20 mg od 3. Placebo Total	 118 118 123 359	 23-78 24-78 20-79 20-79
Astra Merck Trial #100 Multicenter US	TRIAL DESIGN: Two phase, prospective, double-blind, randomized trial in patients with GERD who did not respond to an open-label six week treatment period with standard course of ranitidine 150 mg twice daily. OBJECTIVE: To demonstrate that omeprazole safely and effectively resolves heartburn in patients with pathologic GERD but with no erosive esophagitis on endoscopy.	TRIAL DURATION: Phase 1=6 weeks; Phase 2=8 weeks Phase 1: open label Daily dose ranitidine 150 mg bid Phase 2: double-blind, randomized treatment Daily dose week 1-8: 1. Omeprazole 20 mg od 2. Ranitidine 150 mg bid Total	 533 156 161 533	 19-78 20-88 19-88
Merck Trial #010 Multicenter US This trial counted as 2 trials - Phase 1 as a short term trial and phase 2 as a long term trial	TRIAL DESIGN: Multi-center, double-blind, randomized placebo-controlled trial evaluating the effects of omeprazole 20 mg a.m. or 20 mg a.m. for 3 out of 7 days compared to placebo during 6 months of continued treatment of patients with erosive esophagitis healed following 4-8 weeks of omeprazole 40 mg treatment. OBJECTIVE: To investigate the efficacy of 2 oral omeprazole dosing regimens vs placebo in the treatment of patients with erosive esophagitis healed with 40 mg a.m. and to evaluate the long-term safety of continued omeprazole therapy in patients with healed erosive esophagitis.	TRIAL DURATION: 28 - 32 weeks Phase 1: open-label Daily dose omeprazole 40 mg od Phase 2: 1. Omeprazole 20 mg od 2. Omeprazole 20 mg 3 of 7 days 3. Placebo Total	 472 138 137 131 406	 18-90 18-76 22-80 22-83 18-83
Merck Trial #004 Multicenter US	TRIAL DESIGN: Randomized, double-blind, four-way crossover trial. OBJECTIVE: To investigate the appropriate dose of omeprazole which will control parameters of reflux in a US target population of patients with symptomatic GERD	TRIAL DURATION: Each of the four treatment periods was 5 days with a minimum of 7 days between treatment periods. Treatments: 1. Omeprazole 10 mg a.m. 2. Omeprazole 20 mg a.m. 3. Omeprazole 40 mg a.m. 4. Placebo Total	 13 12 12 13 13	 30-70

Trial No./ Location	Trial Design and Objectives	Treatment Groups	Number of Patients	Age Range
Merck Trial #005 Multicenter US	TRIAL DESIGN: Double-blind dose ranging trial to evaluate two doses of omeprazole vs placebo in healing and symptomatic relief in patients with moderate to severe erosive esophagitis over 4-8 weeks. OBJECTIVE: To investigate the efficacy of two oral dosing regimens of omeprazole vs placebo in healing of erosive esophagitis and the relief of symptoms in patients with moderate or severe GERD; to evaluate the safety of omeprazole in patients with symptomatic moderate or severe GERD	TRIAL DURATION: 4-8 weeks 1. Omeprazole 20 mg od 2. Omeprazole 40 mg od 3. Placebo Total	 93 91 46 230	 20-83 20-79 21-77 20-83

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TABLE 3

Ome Rx Most Common Adverse Events by Treatment
US GERD/Erosive Esophagitis Patients
Short Term (≤12 weeks) Well Controlled/Comparative Trials[a]
Group 2

Adverse Event	Ome Rx[b] (n=613)[c]		Ranitidine (n=161)[c]		Placebo (n=182)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
HEADACHE	45	7.3	12	7.5	10	5.5
DIARRHEA	40	6.5	7	4.3	15	8.2
NAUSEA	21	3.4	10	6.2	9	4.9
SINUSITIS	20	3.3	16	9.9	0	0.0
FLATULENCE	18	2.9	3	1.9	2	1.1
PHARYNGITIS	18	2.9	5	3.1	0	0.0
VOMITING	17	2.8	5	3.1	7	3.8
ABDOMINAL PAIN	14	2.3	8	5.0	2	1.1
RESPIRATORY INFECTON	14	2.3	13	8.1	0	0.0
COUGHING	12	2.0	5	3.1	0	0.0
DIZZINESS	12	2.0	0	0.0	5	2.7
INFECTION VIRAL	11	1.8	5	3.1	1	0.5
COMMON COLD	10	1.6	0	0.0	2	1.1
CONSTIPATION	10	1.6	4	2.5	0	0.0
SGPT INCREASED	10	1.6	1	0.6	2	1.1
FEVER	9	1.5	1	0.6	1	0.5
BACK PAIN	7	1.1	6	3.7	0	0.0
FLU-LIKE DISORDER	6	1.0	1	0.6	0	0.0
SGOT INCREASED	6	1.0	0	0.0	1	0.5
UPPER RESP TRACT INFECTION	6	1.0	0	0.0	3	1.6
URINARY TRACT INFECTION	6	1.0	1	0.6	0	0.0
NO. OF PATIENTS WITH AE	303	49.4	97	60.2	68	37.4

[a] Study AMI #037; #100, Merck #004; #005
[b] Omeprazole treatment includes 10 mg, 20 mg and 40 mg.
[c] Number of subjects randomized to each treatment group.
[d] Number of subjects who reported the adverse event.
[e] Percent of subjects who reported the adverse event: (n/N)*100

Adverse events experienced by at least 1% of the patients in the OME column are given. The adverse events are sorted by the omeprazole column.

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TABLE 4

Ome Rx Most Common Adverse Events by Treatment
US GERD/Erosive Esophagitis Patients
Short Term (≤12 weeks) Controlled and Uncontrolled Trials[a]
Group 4

ADVERSE EVENT	Ome Rx[b] (n=1086)[c]		Ranitidine (n=161)[c]		Placebo (n=182)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
HEADACHE	78	7.2	12	7.5	10	5.5
DIARRHEA	67	6.2	7	4.3	15	8.2
ABDOMINAL PAIN	32	2.9	8	5.0	2	1.1
NAUSEA	29	2.7	10	6.2	9	4.9
FLATULENCE	25	2.3	3	1.9	2	1.1
SINUSITIS	25	2.3	16	9.9	0	0.0
PHARYNGITIS	24	2.2	5	3.1	0	0.0
VOMITING	23	2.1	5	3.1	7	3.8
DIZZINESS	21	1.9	0	0.0	5	2.7
CONSTIPATION	18	1.7	4	2.5	0	0.0
SGPT INCREASED	16	1.5	1	0.6	2	1.1
COUGHING	14	1.3	5	3.1	0	0.0
INFECTION VIRAL	14	1.3	5	3.1	1	0.5
RESPIRATORY INFECTION	14	1.3	13	8.1	0	0.0
BACK PAIN	13	1.2	6	3.7	0	0.0
FEVER	13	1.2	1	0.6	1	0.5
UPPER RESP TRACT INFECTION	12	1.1	0	0.0	3	1.6
NO. OF PATIENTS WITH AE	472	43.5	97	60.2	68	37.4

a) Trial AMI #037; #100, Merck #004; #005, #010
b) Omeprazole treatment includes 10 mg, 20 mg and 40 mg.
c) Number of patients randomized to each treatment group.
d) Number of patients who reported the adverse event.
e) Percent of patients who reported the adverse event: (n/N)*100.

Adverse events experienced by at least 1% of the patients in the Ome column are given. The adverse events are sorted by the omeprazole column.

TABLE 5

Ome Rx Most Common Adverse Events by Indication
US GERD and EE Patients
Short Term (≤12 weeks) Controlled and Uncontrolled Trials
Group 4

Drug:	Ome Rx[a]		Ome Rx[b]		Ome Rx[c]	
Dosage:	10-40 mg Daily		20-40 mg Daily		20-40 mg Daily	
Indication:	GERD or EE		GERD		EE	
No. of patients:	(n=1086)		(n=429)		(n=657)	
No. of patients with AE (%):	637	(58.7)	207	(48.3)	430	(65.4)
HEADACHE	100	(9.2)	25	(5.8)	75	(11.4)
DIARRHEA	89	(8.2)	31	(7.2)	58	(8.8)
NAUSEA	48	(4.4)	14	(3.3)	34	(5.2)
ABDOMINAL PAIN	42	(3.9)	9	(2.1)	33	(5.0)
SINUSITIS	41	(3.8)	19	(4.4)	22	(3.3)
VOMITING	35	(3.2)	11	(2.6)	24	(3.7)
FLATULENCE	30	(2.8)	16	(3.7)	14	(2.1)
PHARYNGITIS	29	(2.7)	14	(3.3)	15	(2.3)
RESPIRATORY INFECTION	27	(2.5)	14	(3.3)	13	(2.0)
DIZZINESS	26	(2.4)	7	(1.6)	19	(2.9)
CONSTIPATION	22	(2.0)	7	(1.6)	15	(2.3)
INFECTION VIRAL	20	(1.8)	4	(0.9)	16	(2.4)
BACK PAIN	19	(1.7)	7	(1.6)	12	(1.8)
COUGHING	19	(1.7)	7	(1.6)	12	(1.8)
SGPT INCREASED	19	(1.7)	1	(0.2)	18	(2.7)
FEVER	15	(1.4)	9	(2.1)	6	(0.9)
UPPER RESP TRACT INFECTION	15	(1.4)	1	(0.2)	14	(2.1)
CHEST PAIN	14	(1.3)	2	(0.5)	12	(1.8)
ACCIDENT AND/OR INJURY	13	(1.2)	4	(0.9)	9	(1.4)
INSOMNIA	13	(1.2)	3	(0.7)	10	(1.5)
COMMON COLD	12	(1.1)	10	(2.3)	2	(0.3)
HEMATURIA	12	(1.1)	4	(0.7)	9	(1.4)
RASH	12	(1.1)	1	(0.2)	11	(1.7)
PYURIA	11	(1.0)	0	(0.0)	11	(1.7)
SGOT INCREASED	11	(1.0)	1	(0.2)	10	(1.5)
TOOTH DISORDER	11	(1.0)	5	(1.2)	6	(0.9)

a) Trial AMI #307; #100, Merck #004, #005, #010.
b) Trial AMI #037; #100, Merck #004.
c) Trial Merck #005, #010

Adverse events experienced by at least 1% of the patients in any column are given. The adverse events are sorted by the omeprazole column.

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TABLE 6
Ome Rx Most Common Adverse Events by Dose and Treatment
US GERD/Erosive Esophagitis Patients
Short Term (≤12 weeks) Controlled and Uncontrolled Trials[a]
Group 4

Adverse Event	OME Rx 10 mg (n=131)[b]		OME Rx 20 mg (n=379)[b]		OME Rx 40 mg (n=576)[b]	
	n[c]	%d	n[c]	%[d]	n[c]	%[d]
HEADACHE	7	5.3	28	7.4	43	7.5
DIARRHEA	8	6.1	28	7.4	31	5.4
NAUSEA	2	1.5	17	4.5	10	1.7
FLATULENCE	3	2.3	14	3.7	8	1.4
ABDOMINAL PAIN	1	0.8	11	2.9	20	3.5
PHARYNGITIS	2	1/5	14	3/8	8	1.4
SINUSITIS	1	-/9	19	4/8	6	1.0
DIZZINESS	3	2.3	7	1.8	11	1.9
COMMON COLD	6	4.6	4	1.1	0	0.0
VOMITING	0	0.0	15	4.0	8	1.4
CONSTIPATION	2	1.5	7	1.8	9	1.6
FEVER	2	1.5	7	1.8	4	0.7
COUGHING	1	0.8	8	2.1	5	0.9
RESPIRATORY INFECTION	0	0.0	14	3.7	0	0.0
BACK PAIN	1	0.8	6	1.6	6	1.0
SGPT INCREASED	0	0.0	6	1.6	10	1.7
INFECTION VIRAL	0	0.0	7	1.8	7	1.2
UPPER RESP TRACT INFECTION	1	0.8	2	0.5	9	1.6
SERUM GLUTAMICOXALOACETIC TA INC	3	2.3	2	0.5	0	0.0
SERUM GLUTAMICPYRUVIC TA INCR	3	2.3	2	0.5	0	0.0
CRAMP ABDOMINAL	3	2.3	1	0.3	0	0.0
HEMATURIA	1	0.8	4	1.1	3	0.5
FLU SYMPTOMS	2	1.5	3	0.8	0	0.0
SINUS CONGESTION	3	2.3	0	0.0	0	0.0
SINUS HEADACHE	3	2.3	0	0.0	0	0.0
SGOT INCREASED	0	0.0	4	1.1	6	1.0
URINARY TRACT INFECTION	1	0.8	5	1.3	0	0.0
CHEST PAIN	0	0.0	3	0.8	7	1.2
FLU-LIKE DISORDER	0	0.0	5	1.3	4	0.7
PYURIA	0	0.0	4	1.1	5	0.9
GASTROENTERITIS	1	0.8	4	1.1	0	0.0
TOOTH DISORDER	1	0.8	4	1.1	0	0.0
BLOATING	2	1.5	1	0.3	0	0.0
JOINT PAIN	2	1.5	1	0.3	0	0.0
RASH	0	0.0	1	0.3	8	1.4
ACCIDENT AND/OR INJURY	0	0.0	5	1.3	2	0.3
PAIN	0	0.0	4	1.1	3	0.5
STRAINED MUSCLE	2	1.5	0	0.0	0	0.0
SWOLLEN HANDS	2	1.5	0	0.0	0	0.0
ABDOMEN ENLARGED	0	0.0	0	0.0	8	1.4
MYALGIA	0	0.0	4	1.1	2	0.3
ERUCTATION	0	0.0	1	0.3	6	1.0
PHOSPHATASE ALKALINE INCREASED	0	0.0	1	0.3	6	1.0
POLYCYTHAEMIA	0	0.0	4	1.1	1	0.2
RHINITIS	0	0.0	4	1.1	1	0.2
FATIGUE	0	0.0	4	1.1	0	0.0
NO. OF PATIENTS WITH AE	56	42.7	201	53.0	215	37.3

a) Trial AMI #037; #100, Merck #004, 005, 010
b) Number of patients within specified treatment category.
c) Number of patients who reported the adverse event within specified treatment category
d) Percent of patients who reported the adverse event within specified treatment category (n/N)*100.
Adverse events experienced by at least 1% of the patients in any column are given.
Adverse events are sorted by the total percentage of OME columns.

TABLE 7

Ome Rx Drug Stopped due to Adverse Events
US GERD/Erosive Esophagitis Subjects
Short Term Studies (≤12 weeks) Controlled and Uncontrolled Studies[a]
Group 4

Drug:	OME Rx[b] (n=1086)[c]		Ranitidine (n=161)[c]		Placebo (n=182)[c]	
Adverse Event	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
DIARRHEA	4	0.4	0	0.0	1	0.5
NAUSEA	4	0.4	0	0.0	1	0.5
VOMITING	4	0.4	0	0.0	0	0.0
ANXIETY	3	0.3	0	0.0	0	0.0
CHEST PAIN	3	0.3	0	0.0	0	0.0
DIZZINESS	3	0.3	0	0.0	1	0.5
HEADACHE	3	0.3	0	0.0	3	1.6
RASH	3	0.3	0	0.0	0	0.0
ABDOMEN ENLARGED	2	0.2	0	0.0	0	0.0
DEPRESSION	2	0.2	0	0.0	0	0.0
INSOMNIA	2	0.2	0	0.0	0	0.0
ABDOMINAL PAIN	1	0.1	0	0.0	0	0.0
ANEMIA	1	0.1	0	0.0	0	0.0
BLOATING	1	0.1	0	0.0	0	0.0
BLOOD PRESSURE LOW	1	0.1	0	0.0	0	0.0
CEREBROVASCULAR ACCIDENT	1	0.1	0	0.0	0	0.0
CORONARY ARTERY DISORDER	1	0.1	0	0.0	0	0.0
COUGHING	1	0.1	0	0.0	0	0.0
DEHYDRATION	1	0.1	0	0.0	0	0.0
DYSPHAGIA	1	0.1	0	0.0	0	0.0
FEVER	1	0.1	0	0.0	0	0.0
GALL BLADDER DISORDER	1	0.1	0	0.0	0	0.0
GASTROENTERITIS ACUTE	1	0.1	0	0.0	0	0.0
LEUKOPENIA	1	0.1	0	0.0	0	0.0
MYOCARDIAL INFARCTION	1	0.1	0	0.0	0	0.0
NUMBNESS	1	0.1	0	0.0	0	0.0
PAIN ARM	1	0.1	0	0.0	0	0.0
PAIN FEET	1	0.1	0	0.0	0	0.0
PANCYTOPENIA	1	0.1	0	0.0	0	0.0
POLYCYTHAEMIA	1	0.1	0	0.0	0	0.0
SGOT INCREASED	1	0.1	0	0.0	0	0.0
SGPT INCREASED	1	0.1	0	0.0	0	0.0
THROMBOCYTOPENIA	1	0.1	0	0.0	0	0.0
URINARY TRACT INFECTION	1	0.1	0	0.0	0	0.0
VASODILATION	1	0.1	0	0.0	0	0.0
VERTIGO	1	0.1	0	0.0	0	0.0
VISION BLURRED	1	0.1	0	0.0	0	0.0
NO. OF PATIENTS WITH AE	24	2.2	0	0.0	5	2.7

a) Trial AMI #037; #100, Merck, #004; #005, #010.
b) Omeprazole treatment includes 10 mg, 20 mg and 40 mg.
c) Number of subjects randomized to each treatment group.
d) Number of subjects who reported the adverse event.
e) Percent of subjects who reported the adverse event: (n/N)*100.

Adverse Events are sorted in decreasing order of frequency to 0.1% in OME column.

TABLE 8

OME Rx Drug Stopped Due to Adverse Events
Non-US GERD/Erosive Esophagitis Patients
All Long Term (>12 weeks) Trials
Groups 5 & 7

DRUG: DOSAGE:	OME Rx[a] 10-40 mg daily or 29 ng*3/ Weekend or 10-20 mg daily on Demand		Ranitidine[b] 150-300 mg daily		Placebo[c]	
No. of Patients: No. of Patients With Drug Stoped Due to AE (%):	(n=1235) 46	(3.7)	(n=201) 7	(3.5)	(n=286) 28	(9.8)
DIARRHEA	6	(0.5)	0		1	(0.3)
ABDOMINAL PAIN	5	(0.4)	0		0	
DUS[E]SOA	5	(0.4)	0		15	(5.2)
FLATULENCE	4	(0.3)	0		1	(0.3)
EPIGASTRIC PAIN	3	(0.2)	1	(0.5)	5	(1.7)
URTICARIA	3	(0.2)	0		0	
ANGINA PECTORIS	2	(0.2)	0		0	
CONSTIPATION	2	(0.2)	0		1	(0.3)
GASTROESOPHAGEAL REFLUX	2	(0.2)	0		3	(1.0)
HEADACHE	2	(0.2)	0		0	
MYOCARDIAL INFARCTION	2	(0.2)	0		0	
NAUSEA	2	(0.2)	1	(0.5)	0	
PRURITUS	2	(0.2)	0		0	
ANGIOEDEMA	1	(0.1)	0		0	
ASTHENIA	1	(0.1)	0		0	
BRONCHITIS	1	(0.1)	0		0	
CHEST PAIN	1	(0.1)	0		0	
COLON CARCINOMA	1	(0.1)	0		0	
COMA HEPATIC	1	(0.1)	0		0	
DERMATITIS	1	(0.1)	0		1	(0.3)
DIZZINESS/VERTIGO	1	(0.1)	1	(0.5)	1	(0.3)
DYSPHAGIA	1	(0.1)	0		1	(0.3)
DYSPNEA	1	(0.1)	0		0	
EARACHE	1	(0.1)	0		0	
EMBOLISM PULMONARY	1	(0.1)	0		0	
ERUCTATION	1	(0.1)	0		1	(0.3)
FATIGUE	1	(0.1)	0		0	
HUNGER PANGS	1	(0.1)	0		0	
INTESTINAL PERFORATION	1	(0.1)	0		0	
IRRITABLE BOWEL	1	(0.1)	0		0	
NEPHRITIS INTERSTITIAL	1	(0.1)	0		0	
ODEMA LEGS	1	(0.1)	0		0	
ESOPHAGEAL STRICTURE	1	(0.1)	0		0	
PAIN	1	(0.1)	0		0	
PAROTID NEOPLASM	1	(0.1)	0		0	
RASH ERYTHEMATOUS	1	(0.1)	0		0	
RASH MACULO-PAPULAR	1	(0.1)	0		0	
SOMNOLENCE	1	(0.1)	0		0	
YAWNING	1	(0.1)	0		0	

a) I-613B. I-621B, I-627B, I-640B, I-640C, I-640D, I-641B, I-641C, I-1601B, I-1602B
b) I-613B, I-621B, I-641B
c) I-640B, I-1602B

The adverse events are listed in decreasing order of frequency to 0.1% in the omeprazole column.

TABLE 9

OME Rx Related, Non-Fatal Serious Adverse Events
Non-US GERD/Erosvie Esophagitis/Dyspepsia Patients
Short Term (≤12 weeks) Controlled and Uncontrolled Trials
Group 3

DRUG:	OME RX [a]	RANITIDINE [b]	PLACEBO [c]
DOSAGE:	10 - 40 MG DAILY	150 - 300 MG DAILY	-
NO. OF PATIENTS:	(N=4671)	(N=926)	(N=943)
NO. OF PATIENTS WITH RELATED NON-FATAL SAE (%):	3 (0.1)	0 (0.0)	0 (0.0)
Arthralgia/Enterocoliti	1 (0.0)	0	0
Bronchospasm	1 (0.0)	0	0
Nephritis interstitial	1 (0.0)	0	0

a I-603, I-605A, I-606, I-608A, I-609A, I-609B, I-613A, I-619, I-621A, I-627A, I-640A, I-641A, I-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0003, SH-OMD-0007, SH-OMD-0008
b I-603, I-605A, I-606, I-608A, I-613A, I-619, I-1602A, I-1603, SH-OMD-0001
c I-609A, I-1601A, I-1603, SH-OMD-0001, SH-OMD-0003, SH-OMD-0007, SH-OMD-0008
FOR PATIENTS WITH MORE THAN ONE NON-FATAL SAE, THE COMBINATION OF SUCH AE PER PATIENT IS GIVEN.

APPEARS THIS WAY
ON ORIGINAL

TABLE 10

OME Rx Serious Adverse Events
US GERD/Erosive Esophagitis Patients
Short Term (≤12 weeks) Controlled and Uncontrolled Trials[a]
Group 4

DRUG No. of Patients: Adverse Event	OME Rx[b] (n=1062)[c]		Ranitidine (n=161)[c]		Placebo (n=182)[c]	
	n[d]	%[e]	n[d]	%[e]	n[d]	%[e]
NAUSEA	5	0.5	0	0.0	0	0.0
VOMITING	5	0.5	0	0.0	0	0.0
BODY ACHE	2	0.2	0	0.0	0	0.0
CHEST PAIN	2	0.2	0	0.0	0	0.0
DIARRHEA	2	0.2	0	0.0	0	0.0
FEVER	2	0.2	0	0.0	0	0.0
ANEMIA	1	0.1	0	0.0	0	0.0
APPENDICITIS	1	0.1	1	0.6	0	0.0
ARTHROSIS	1	0.1	0	0.0	0	0.0
ASTHMA	1	0.1	0	0.0	0	0.0
ATELECTASIS	1	0.1	0	0.0	0	0.0
BLOOD PRESSURE LOW	1	0.1	0	0.0	0	0.0
CEREBROVASCULAR ACCIDENT	1	0.1	0	0.0	0	0.0
CHOLECYSTITIS	1	0.1	0	0.0	0	0.0
CONSTIPATION	1	0.1	0	0.0	0	0.0
CORONARY ARTERY DISORDER	1	0.1	0	0.0	0	0.0
DEHYDRATION	1	0.1	0	0.0	0	0.0
DIZZINESS	1	0.1	0	0.0	0	0.0
DYSPHAGIA	1	0.1	0	0.0	0	0.0
DYSPNEA	1	0.1	0	0.0	1	0.5
EAR DISORDER NOS	1	0.1	0	0.0	0	0.0
ENCEPHALOPATHY	1	0.1	0	0.0	0	0.0
EPIGASTRIC PAIN	1	0.1	0	0.0	0	0.0
FLATULENCE	1	0.1	0	0.0	0	0.0
FRACTURE PATHOLOGICAL	1	0.1	0	0.0	0	0.0
GALL BLADDER DISORDER	1	0.1	1	0.6	0	0.0
GASTROENTERITIS ACUTE	1	0.1	0	0.0	0	0.0
HERNIA	1	0.1	0	0.0	0	0.0
HERNIA INGUINAL	1	0.1	0	0.0	0	0.0
INFECTION BACTERIAL	1	0.1	0	0.0	0	0.0
LEUKOPENIA	1	0.1	0	0.0	0	0.0
MYOCARDIAL INFARCTION	1	0.1	0	0.0	0	0.0
NUMBNESS	1	0.1	0	0.0	0	0.0
PAIN ARM	1	0.1	0	0.0	0	0.0
PAIN FEET	1	0.1	0	0.0	0	0.0
PAIN RIGHT UPPER QUADRANT	1	0.1	0	0.0	0	0.0
PANCREATITIS	1	0.1	0	0.0	0	0.0
PANCYTOPENIA	1	0.1	0	0.0	0	0.0
POLYCYTHAEMIA	1	0.1	0	0.0	0	0.0
SKIN DISORDER	1	0.1	0	0.0	0	0.0
SWEATING INCREASED	1	0.1	0	0.0	0	0.0
THROMBOCYTOPENIA	1	0.1	0	0.0	0	0.0
URINARY TRACT INFECTION	1	0.1	0	0.0	0	0.0
VERTIGO	1	0.1	0	0.0	0	0.0
ABDOMINAL PAIN	0	0.0	1	0.6	0	0.0
ACCIDENT AND/OR INJURY	0	0.0	1	0.6	0	0.0
CARCINOMA	0	0.0	1	0.6	0	0.0
COGNITIVE IMPAIRMENT	0	0.0	1	0.6	0	0.0

ANGINAL ATTACK	0	0.0	0	0.0	1	0.5
PNEUMONIA	0	0.0	0	0.0	1	0.5
TRABSUTIRT USCGENUC ATTACJ	0	0.0	0	0.0	1	0.5
NO. OF PATIENTS WITH AE	20	1.9	5	3.1	3	1.6

a) Trial AMI #037, #100, Merck #004, #005, #010.
b) Omeprazole treatment includes 10 mg, 20 mg and 40 mg.
c) Number of patients randomized to each treatment group.
d) Number of patients who reported the adverse event.
e) Percent of patients who reported the adverse event: (n/N)100.

The adverse events are sorted by the omeprazole column in decreasing order of frequency.

/s/

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