# 7 Summary of Safety

This section will summarize the safety data from the OTC clinical program and will provide a similar summary from the Rx clinical program. In addition, post-marketing surveillance data will be presented.

The OTC clinical safety consists of 11,790 subjects from 11 studies ranging in use from 1 day to 4 weeks. Both 10 mg and 20 mg doses were evaluated. The Rx clinical safety consists of 7,500 subjects in 35 clinical trials with use from 1 day to 1 year. Doses of 10 mg to 40 mg were evaluated. The post-marketing data summarizes worldwide reports from 1988 until July 1998. In this time, approximately 300 million courses of patient treatments have been prescribed in 103 countries.

## 7.1 OTC Omeprazole Magnesium Clinical Trial Adverse Events

This section provides a review of all OTC clinical trials in which Ome-Mg tablets were administered. A total of 11 US studies conducted by AstraZeneca LP and The Procter & Gamble Company (P&G), have contributed to the safety database. These studies were carried out over a 2-year period. A total of 8,670 subjects in the safety database used Ome-Mg for a single dose to more than 4 weeks of treatment duration. Of the 8,670 subjects, 5,040 subjects took Ome-Mg 20 and 3,630 subjects took Ome-Mg 10. In addition, 3,120 subjects received placebo.

Six of these 11 studies were controlled trials (Studies 171, 183, 005, 006, 092, and 095) comprised of subjects with a history of self-limited heartburn and without a physician diagnosis of GERD. Four other studies (Studies 003, 022, 067, and 014) were consumer research studies conducted to gather consumer use pattern data. There were no placebo or comparator arms in these four studies. For the purposes of this safety section of this briefing document, these consumer research studies will be referred to as the uncontrolled trials. The uncontrolled trials were comprised of subjects who self-selected to use the study medication or who had a history of antacid or $H_2$RA use in the last month, and did not exclude subjects with GERD. The eleventh study was a 3-way cross-over PK study (Study 200) that compared the Ome-Mg formulation with the Ome capsule formulation in normal healthy subjects.

### 7.1.1 Adverse Events

#### 7.1.1.1 Comprehensive

Table 7.1 provides a summary of AE frequency by dose for the OTC clinical trials. The percentage of subjects reporting one or more AEs was comparable across all treatment groups within each study. In general, for the uncontrolled clinical trials the percentage of subjects with AE's was greater than in the controlled trials, a phenomenon commonly seen in studies in which the subjects know they are receiving an active compound. Further, the duration of the uncontrolled studies was longer.

**TABLE 7.1**
**OMEPRAZOLE MAGNESIUM CLINICAL TRIALS**
**NUMBER (%) OF SUBJECTS REPORTING ONE OR MORE AES**
**BY CLINICAL TRIAL AND TREATMENT GROUP**

| **Clinical Trial** | **Treatment Group** | | |
|---|---|---|---|
| **Controlled Study*** | **Ome-Mg 20** | **Ome-Mg 10** | **Placebo** |
| 005 (single dose) | 24/433 (6%) | 34/430 (8%) | 27/423 (6%) |
| 006 (single dose) | 11/394 (3%) | 15/387 (4%) | 9/390 (2%) |
| 092 (2 weeks) prn | 82/628 (13%) | 72/636 (11%) | 71/635 (11%) |
| 095 (2 weeks) prn | 82/638 (13%) | 85/633 (13%) | 93/621 (15%) |
| 171 (2 weeks dosing, 2-week placebo follow-up) daily | 144/528 (27%) | 123/527 (23%) | 144/526 (22%) |
| 183 (2 weeks dosing, 2-week placebo follow-up) daily | 127/525 (24%) | 146/526 (28%) | 128/525 (24%) |
| **TOTAL** | **470/3146 (15%)** | **475/3139 (15%)** | **442/3120 (14%)** |
| **Uncontrolled Study** | **Ome-Mg 20** | **Ome-Mg 10** | **Placebo** |
| 003 (4 weeks) prn | 203/833 (24%) | — | — |
| 022 (4 weeks) prn | — | 139/491 (28%) | — |
| 067 (4 weeks) prn | 51/92 (55%) | — | — |
| 014 (4 weeks) prn | 329/939 (35%) | — | — |
| 200 (3-way crossover) | 2/30 (7%) | — | — |
| **TOTAL** | **585/1894 (31%)** | **139/491 (28%)** | |

*Double-Blind, Placebo-Controlled

Figure 7.1 and Table 7.2 display the most commonly reported AEs for the controlled clinical trials. Of the 9,349 subjects who took at least one dose of study drug in the controlled trials, 6,252 subjects were treated with Ome-Mg 20 or Ome-Mg 10.

Similarly, Figure 7.2 and Table 7.3 display the most commonly reported AEs for the uncontrolled clinical trials. Of the 2,385 subjects participating in the uncontrolled trials, the majority (1,894) were treated with Ome-Mg 20.

In the double-blind, placebo-controlled clinical trials, 15% of the Ome-Mg 10 and Ome-Mg 20 treated subjects and 14% of the placebo-treated subjects reported at least one AE, whereas in the uncontrolled trials, approximately 30% of the subjects reported at least one AE. With the exception of the PK study (Study 200), possible reasons for the higher AE incidence in the uncontrolled trials included duration of medication exposure, method of AE collection, and subjects' understanding during the uncontrolled trials that they were receiving active medication. Headache, infection, and diarrhea were the most commonly reported AEs across all treatment groups, with the exception of the uncontrolled clinical trials, where abdominal pain was reported more often than diarrhea in the Ome-Mg 20 group.

Thus, the data indicate that the incidence of AEs was similar between the Ome-Mg-treated groups and the placebo group. In addition, there is no dose-response increase in AE reporting between the Ome-Mg 10 and Ome-Mg 20 treatment groups.

**FIGURE 7.1**
**MOST COMMON ADVERSE EVENTS**
**OTC CONTROLLED STUDIES**

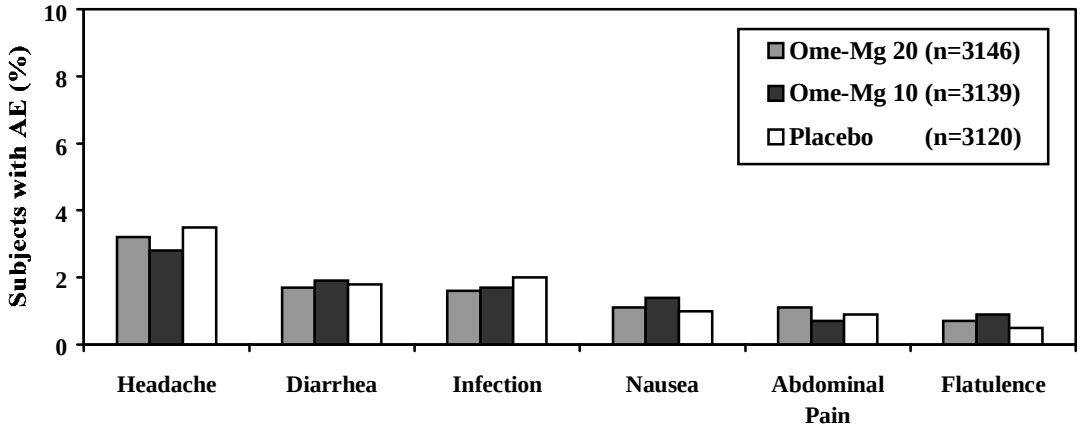


**FIGURE 7.2**
**MOST COMMON ADVERSE EVENTS**
**OTC UNCONTROLLED STUDIES**

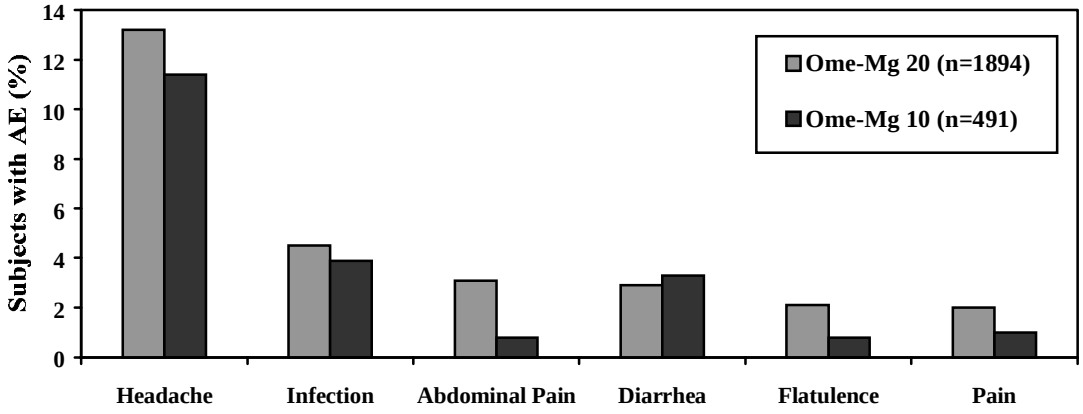

**TABLE 7.2**
**ADVERSE EVENTS FOR OME-MG[a] AND PLACEBO OTC SUBJECTS IN CONTROLLED STUDIES[b]**
**SUMMARY BY COSTART AND TREATMENT**
**DESCENDING TO ONE PERCENT**

| COSTART Term | Ome-Mg 20 (N =3146)[c] | | Ome-Mg 10 (N = 3139)[c] | | Placebo (N = 3120)[c] | |
|---|---|---|---|---|---|---|
| | n[d] | %[e] | n[d] | %[e] | n[d] | %[e] |
| **Total Number of Subjects with One or More AEs** | 470 | 15% | 475 | 15% | 442 | 14% |
| Headache | 102 | 3% | 87 | 3% | 109 | 3% |
| Diarrhea | 54 | 2% | 59 | 2% | 56 | 2% |
| Infection | 51 | 2% | 53 | 2% | 62 | 2% |
| Nausea | 36 | 1% | 43 | 1% | 30 | 1% |
| Pain Abdominal | 35 | 1% | 22 | 1% | 29 | 1% |
| Flatulence | 22 | 1% | 27 | 1% | 14 | <1%[f] |
| Pain Back | 21 | 1% | 19 | 1% | 16 | 1% |
| Vomiting | 19 | 1% | 21 | 1% | 18 | 1% |
| Pharyngitis | 19 | 1% | 15 | <1%[f] | 12 | <1%[f] |
| Flu Syndrome | 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% | 18 | 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 AEs within specified Treatment Group and COSTART.

[e] Percent of subjects who reported AEs 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 20 column.

**TABLE 7.3**
**ADVERSE EVENTS FOR OME-MG[a] OTC SUBJECTS IN UNCONTROLLED STUDIES[b]**
**SUMMARY BY COSTART AND TREATMENT**
**DESCENDING TO ONE PERCENT**

| COSTART Term | Ome-Mg 20 (N = 1894)[c] | | Ome-Mg 10 (N = 491)[c] | |
|---|---|---|---|---|
| | n[d] | %[e] | n[d] | %[e] |
| **Total Number of Subjects with One or More AEs** | 585 | 31% | 139 | 28% |
| Headache | 250 | 13% | 56 | 11% |
| Infection | 86 | 5% | 19 | 4% |
| Pain Abdominal | 58 | 3% | 9 | 2% |
| Diarrhea | 54 | 3% | 16 | 3% |
| Flatulence | 39 | 2% | 4 | 1% |
| Pain | 38 | 2% | 9 | 2% |
| Nausea | 33 | 2% | 4 | 1% |
| Pain Back | 30 | 2% | 11 | 2% |
| Dyspepsia | 28 | 1% | 2 | <1% |
| Flu Syndrome | 27 | 1% | 0 | 0% |
| Dizziness | 17 | 1% | 1 | <1% |
| Pharyngitis | 15 | 1% | 4 | 1% |
| Myalgia | 14 | 1% | 5 | 1% |
| Cough Increased | 13 | 1% | 1 | <1% |
| Sinusitis | 13 | 1% | 3 | 1% |
| Constipation | 12 | 1% | 4 | 1% |
| Insomnia | 11 | 1% | 2 | <1% |
| Rhinitis | 11 | 1% | 5 | 1% |
| Injury Accidental | 10 | 1% | 2 | <1% |

[a] Ome-Mg (omeprazole magnesium) treatment includes both 10.3 mg and 20.6 mg.

[b] Includes subjects from the following uncontrolled studies: P&G 1998003, 1998014, 1999022, 1998067; AMI 200 (only includes data from periods where tablet formulation was taken).

[c] Number of subjects evaluable for safety.

[d] Number of subjects who reported AEs within specified Treatment Group and COSTART.

[e] Percent of subjects who reported AEs within specified Treatment Group and COSTART: (n/N)*100.

### 7.1.1.2 Subgroup Assessment

Subgroup assessment (by gender, by age, and by race) revealed no clinically meaningful inter-treatment differences. A greater percentage of subjects reported one or more AEs in the 12–17 age group; however, this may be related to the fact that the majority of adolescent subjects (96%) were enrolled in an open-label study (067) that was conducted during flu season.

## 7.1.2 Discontinuations Due to Adverse Events

Table 7.4 presents a summary of study discontinuations due to AEs in the OTC clinical trials by dose and gender (controlled and uncontrolled combined). The incidence of discontinuations due to AEs was low and similar across dose groups and gender. A total of 64 subjects, 46 Ome-Mg (0.5%) and 18 placebo (0.6%) discontinued study participation due to an AE. The AEs most commonly reported as causing discontinuation were headache, nausea, and vomiting in the Ome-Mg treated groups, and diarrhea, abdominal pain, and nausea in the placebo-treated group.

**TABLE 7.4**
**DISCONTINUATIONS DUE TO ADVERSE EVENTS IN THE CLINICAL TRIALS, SAFETY EVALUABLE POPULATION**
**(INCLUDES STUDIES 171, 183, 003, 005, 006, 014, 022, 092, 095)**

| Treatment | Trial N | Discontinued | Male | Female | Unlikely | Possible | Probable |
|---|---|---|---|---|---|---|---|
| Placebo | 3120 | 18 (0.6%) | 6 (0.2%) | 12 (0.4%) | 10 (0.2%) | 5 (0.2%) | 3 (0.1%) |
| Ome-Mg 10 | 3630 | 18 (0.5%) | 9 (0.2%) | 9 (0.2%) | 11 (0.3%) | 7 (0.1%) | 0 (0.0%) |
| Ome-Mg 20 | 5040 | 28 (0.6%) | 11 (0.2%) | 17 (0.3%) | 7 (0.1%) | 16 (0.3%) | 5 (0.1%) |

Source: NDA, Section 8.8.2, Table 22a

## 7.1.3 Deaths

There were two deaths (incidence of 0.017%) during the clinical trials with Ome-Mg. Both were unrelated to the use of study medication: one was a suicide (involving multiple drugs), and the other was attributed to a heroin overdose.

## 7.1.4 Other Non-Fatal Serious Adverse Events

Table 7.5 presents a summary of subjects by dose and gender who experienced SAE(s) in the OTC clinical trials. The incidence of SAEs was low and comparable across dose groups, and with but two exceptions, the SAEs were considered by the investigation unrelated to study medication. One subject, a 35-year-old Caucasian female, was randomized to receive Ome-Mg 10 (Study 092) and subsequently developed serum sickness (angioedema). A second subject (Study 183) developed esophagitis and gastritis (both assessed as possibly related); this subject was randomized to placebo treatment.

In addition to the above, there were 6 subjects who reported SAEs during the placebo run-in phases for Studies 171, 183, 092, and 095. These 6 subjects included 3 females and 3 males. All of these SAEs were considered by the investigator unlikely to be related to study medication.

**TABLE 7.5**
**NUMBER (%) OF SUBJECTS WITH SERIOUS ADVERSE EVENTS IN THE OTC CLINICAL TRIALS**
**(INCLUDES STUDIES 171, 183, 003, 005, 006, 014, 092, 095, 022)**

| Treatment | Trial N | No. Subjects with SAE | Male | Female | Unlikely | Possible | Probable |
|---|---|---|---|---|---|---|---|
| Placebo | 3120 | 4 (0.1%) | 2 (0.1%) | 2 (0.1%) | 3 (0.1%) | 1 (0.03%) | 0 (0.0%) |
| Ome-Mg 10 | 3630 | 15 (0.4%) | 3 (0.1%) | 12 (0.3%) | 14 (0.4%) | 0 (0.0%) | 1 (0.03%) |
| Ome-Mg 20 | 5040 | 12 (0.2%) | 6 (0.1%) | 6 (0.1%) | 12 (0.2%) | 0 (0.0%) | 0 (0.0%) |

### 7.1.5 Laboratory Safety

Laboratory data were collected before and after dosing in Studies 171 and 183. There were no notable laboratory findings of clinical concern in any treatment group.

## 7.2 Prescription Omeprazole (Ome) Clinical Trial Adverse Events

This section presents a review of AEs from Rx clinical trials in which Ome was used to treat GERD, EE and dyspepsia. Six US trials conducted by Astra Merck Inc. (AMI) and Merck and Co., Inc. (Merck) along with 29 non-US clinical trials conducted by Astra Hässle (Astra), evaluated over 7,500 patients and comprised the Rx safety database assembled for the NDA. A total of 5,757 unique patients were exposed to Ome in these clinical trials. This group of patients more closely resembles the targeted OTC population than other patient populations studied in Rx clinical trials with Ome (e.g., patients with severe hypersecretory conditions such as ZES). These 35 clinical trials however, included uncontrolled studies of various designs. The data pooled from these 35 trials will be briefly discussed but not presented in this document. For the purpose of this document and in an effort to provide the AE data in a scientific fashion, allowing quantitative assessment of AEs, safety data will be presented from well-controlled trials only.

### 7.2.1 Patient Disposition, Overall Extent of Exposure, and Demographic Characteristics

#### 7.2.1.1 Patient Disposition and Overall Extent of Exposure

**<u>All Trials — Controlled and Uncontrolled</u>**

The 35 trials described above were divided into non-US or US, short-term (≤12 weeks of treatment) or long-term (>12 weeks of treatment).

**29 Non-US Studies — Controlled and Uncontrolled Studies Combined**
A total of 4,671 unique Ome patients are represented in the non-US short and long-term GERD, EE and dyspepsia trials. Of those patients, 1,235 continued into a long-term trial upon completion of a short-term trial.

**6 US Studies — Controlled and Uncontrolled Studies Combined**
A total of 1,086 unique Ome patients are represented in the US short-and long-term GERD and EE trials. Of those patients, 406 continued into a long-term trial upon completion of a short-term trial (there is only one long-term trial in the US grouping).

**Well Controlled Studies Only**

The US and Non-US *well controlled* trial data, pooled for presentation, includes 14 Non-US (3269 patients) and 4 US (613 patients) studies. Short and long term data are presented separately in order to observe AE occurrence during short term treatment, more reflective of the OTC consumer usage pattern, and also to observe any duration dependent effects of long term treatment on the AE profile of Ome. Doses ranged from 10 mg to 40 mg with duration of treatment from 1 day to 12 weeks for short-term trials and a duration of treatment from greater than 12 weeks to 1 year for long-term trials. The US and non-US data are reported separately due to some differences in the dictionaries employed at the time the trials were conducted.

### 7.2.1.2 Demographic Characteristics

**Short-Term Trials Demography — All Trials (Controlled and Uncontrolled)**

Overall when all trials are pooled (controlled and uncontrolled) subjects in the non-US and US short-term trials were demographically similar, with the exception of a slightly higher percentage of males in the US trials (64%) as compared to the non-US trials (51%). The non-US data only identify age range as ≥65 or <65 and have no breakdown by race because the non-US trial population were almost all Caucasians. The demographics for GERD and EE are similar in both Non-US and US trial groups. The dyspepsia studies (non-US only) have a higher percentage of females compared to the GERD and EE trials as well as a lower percentage of elderly patients.

**Long Term Trials Demography — All Trials (Controlled and Uncontrolled)**

The non-US and US long-term groups (pooling of all controlled and uncontrolled trials) also show no clinically relevant demographic differences between US and non-US. There are only GERD and EE trials in the non-US long-term grouping and only one trial (EE) in the long-term US grouping. The EE trials show more males than females when compared to the GERD trials.

### 7.2.2 Prescription Trials Safety Data — Well Controlled Studies

As noted above, in an effort to provide the AE data in a scientific fashion, allowing quantitative assessment of AEs, safety data will be presented from well-controlled trials only. Table 7.6 through Table 7.11 present a summary of subjects with AEs, as well as the 10 most commonly reported AEs in the US and non-US short-term and long-term controlled trials, for GERD, EE, and dyspepsia. AEs have been sorted by the column entitled "Ome Rx in Controlled Trials."

Diarrhea and headache were the most frequently reported AEs for subjects who took Ome. Subjects receiving Ome did not demonstrate a clinically relevant increased rate of AE reporting for any individual AE when compared to subjects treated with placebo or ranitidine. The overall AE experience in well-controlled trials involving the indications of GERD, EE, and dyspepsia, demonstrates that the safety profile for Ome is similar to that of placebo and an active comparator (ranitidine).

After a careful review of both long- and short-term data, it was concluded that the AE profile for the non-US long-term clinical trials is comparable to that of short-term trials. In the non-US long-term trials the safety profile of Ome did not demonstrate increases in the number of AEs disproportionate to the duration of treatment. The one long-term US trial reported significantly more clinical AEs for the Ome group vs. placebo. A life-table analysis of the temporal distribution of clinical AEs

indicated that there was no significant difference between Ome and placebo. Thus the increased number of AEs reported with Ome reflected the longer average duration of study participation (Ome 20 mg groups 137 and 98 days) vs. placebo (46 days).

**TABLE 7.6**
**OME RX MOST COMMON ADVERSE EVENTS BY TREATMENT**
**NON-US GERD/EROSIVE ESOPHAGITIS/DYSPEPSIA PATIENTS**
**SHORT TERM (≤12 WEEKS) WELL CONTROLLED/COMPARATIVE TRIALS**

| **Drug:** | **Ome Rx** [a] | **Ranitidine** [a] |
|---|---|---|
| **Dosage:** | **10–40 mg daily** | **150–300 mg daily** |
| **No. of patients:** | **(n=1464)** | **(n=926)** |
| **No. of patients with AE (%):** | **426 (29.1%)** | **281 (30.3%)** |
| Diarrhea | 47 (3.2%) | 29 (3.1%) |
| Headache | 47 (3.2%) | 23 (2.5%) |
| Respiratory infection | 33 (2.3%) | 20 (2.2%) |
| Abdominal pain | 31 (2.1%) | 15 (1.6%) |
| Flatulence | 31 (2.1%) | 17 (1.8%) |
| Dizziness/vertigo | 29 (2.0%) | 13 (1.4%) |
| Pharyngitis | 28 (1.9%) | 13 (1.4%) |
| Nausea/nausea (aggravated) | 22 (1.5%) | 16 (1.7%) |
| Constipation | 19 (1.3%) | 17 (1.8%) |
| Pain | 16 (1.1%) | 7 (0.8%) |
| Back pain | 15 (1.0%) | 7 (0.8%) |
| Rhinitis | 14 (1.0%) | 6 (0.6%) |
| Infection viral | 13 (0.9%) | 7 (0.8%) |
| Vomiting/vomiting (aggravated) | 13 (0.9%) | 15 (1.6%) |
| Mouth dry | 5 (0.3%) | 10 (1.1%) |

[a] I-603, I-605A, I-606, I-608A, I-613A, I-619, I-1602A, SH-OMD-0001
AEs experienced by at least 1.0% of the patients in any column are given. The AEs are sorted by the omeprazole column.

**TABLE 7.7**
**OME RX MOST COMMON ADVERSE EVENTS BY TREATMENT**
**NON-US GERD/EROSIVE ESOPHAGITIS/DYSPEPSIA PATIENTS**
**SHORT TERM (≤12 WEEKS) PLACEBO CONTROLLED**

| **Drug:** | **Ome Rx** [a] | **Placebo** [a] |
|---|---|---|
| **Dosage:** | **10–40 mg daily** | **-** |
| **No. of patients:** | **(n=2200)** | **(n=943)** |
| **No. of patients with AE (%):** | **588 (26.7%)** | **209 (22.2%)** |
| Diarrhea | 80 (3.6%) | 24 (2.5%) |
| Headache | 75 (3.4%) | 36 (3.8%) |
| Respiratory infection | 51 (2.3%) | 22 (2.3%) |
| Abdominal pain | 37 (1.7%) | 10 (1.1%) |
| Flatulence | 36 (1.6%) | 3 (0.3%) |
| Nausea/nausea (aggravated) | 36 (1.6%) | 7 (0.7%) |
| Dizziness/vertigo | 28 (1.3%) | 11 (1.2%) |
| Constipation | 28 (1.3%) | 12 (1.3%) |
| Back Pain | 24 (1.1%) | 7 (0.7%) |
| Infection viral | 20 (0.9%) | 10 (1.1%) |
| Pharyngitis | 19 (0.9%) | 4 (0.4%) |
| Vomiting/vomiting (aggravated) | 16 (0.7%) | 6 (0.6%) |
| Pain | 14 (0.6%) | 7 (0.7%) |
| Rhinitis | 13 (0.6%) | 4 (0.4%) |
| Mouth dry | 4 (0.2%) | 3 (0.3%) |

[a] I-609A, I-1601A, I-1603, SH-OMD-0001, SH-OMD-0003, SH-OMD-0007, SH-OMD-0008
AEs experienced by at least 1.0% of the patients in any column are given. The AEs are sorted by the omeprazole column.

**TABLE 7.8**
**OME RX MOST COMMON ADVERSE EVENTS BY TREATMENT**
**US GERD/EROSIVE ESOPHAGITIS PATIENTS**
**SHORT TERM (≤ 12 WEEKS) WELL CONTROLLED/COMPARATIVE TRIALS[a]**

| Adverse Event | Ome Rx[b] (n =613) | Ranitidine (n =161) | Placebo (n =182) |
|---|---|---|---|
| **Number. Of Subjects with AE** | **303 (49.4%)** | **97 (60.2%)** | **68 (37.4%)** |
| 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 Infection | 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 (15%) | 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 Respiratory Tract Infection | 6 (1.0%) | 0 (0.0%) | 3 (1.6%) |
| Urinary Tract Infection | 6 (1.0%) | 1 (0.6%) | 0 (0.0%) |

[a] Trial AMI #037; #100, Merck #010

[b] Omeprazole treatment includes 10 mg, 20 mg, and 40 mg.

The AEs are sorted by the omeprazole column.

**TABLE 7.9**
**OME RX TEN MOST COMMON ADVERSE EVENTS BY TREATMENT**
**NON-US GERD/EROSIVE ESOPHAGITIS PATIENTS**
**LONG TERM (>12 WEEKS) WELL CONTROLLED/COMPARATIVE TRIALS**

| **Drug:** | **Ome Rx** [a] | **Ranitidine** [a] |
|---|---|---|
| **Dosage:** | **10–20 mg daily** | **150–300 mg daily** |
| **No. of patients:** | **(n=362)** | **(n=201)** |
| **No. of patients with AE (%):** | **202 (55.8%)** | **94 (46.8%)** |
| Epigastric pain | 29 (8.0%) | 15 (7.5%) |
| Diarrhea | 20 (5.5%) | 5 (2.5%) |
| Abdominal pain | 15 (4.1%) | 4 (2.0%) |
| Nausea | 14 (3.9%) | 7 (3.5%) |
| Back pain | 12 (3.3%) | 5 (2.5%) |
| Flatulence | 12 (3.3%) | 4 (2.0%) |
| Fatigue | 11 (3.0%) | 2 (1.0%) |
| Chest pain | 10 (2.8%) | 3 (1.5%) |
| Mouth dry | 9 (2.5%) | 4 (2.0%) |
| Pain | 9 (2.5%) | 2 (1.0%) |

[a] I-613B, I-621B, I-641B

The AEs are sorted by the omeprazole column.

**TABLE 7.10**
**OME RX TEN MOST COMMON ADVERSE EVENTS BY TREATMENT**
**NON-US GERD/EROSIVE ESOPHAGITIS PATIENTS**
**LONG TERM (>12 WEEKS) PLACEBO CONTROLLED TRIALS**

| **Drug:** | **Ome Rx** [a] | **Placebo** [a] |
|---|---|---|
| **Dosage:** | **10–20 mg daily** | **-** |
| **No. of patients:** | **(n=377)** | **(n=286)** |
| **No. of patients with AE (%):** | **196 (52.0%)** | **159 (55.6%)** |
| Pain | 19 (5.0%) | 8 (2.8%) |
| Nausea | 17 (4.5%) | 6 (2.1%) |
| Back pain | 17 (4.5%) | 5 (1.7%) |
| Diarrhea | 16 (4.2%) | 12 (4.2%) |
| Abdominal pain | 12 (3.2%) | 3 (1.0%) |
| Epigastric pain | 7 (1.9%) | 5 (1.7%) |
| Flatulence | 7 (1.9%) | 5 (1.7%) |
| Chest pain | 4 (1.1%) | 2 (0.7%) |
| Fatigue | 3 (0.8%) | 1 (0.3%) |
| Mouth dry | 2 (0.5%) | 2 (0.7%) |

[a] I-640B, I-1602B

The AEs are sorted by the omeprazole column.

**TABLE 7.11**
**OME RX MOST COMMON ADVERSE EVENTS BY TREATMENT**
**US EROSIVE ESOPHAGITIS PATIENTS**
**LONG TERM (>12 WEEKS) PLACEBO CONTROLLED TRIAL[a]**

| | OME RX[b] (N =275) | | Placebo (N =131) | |
|---|---|---|---|---|
| **Adverse Event** | **N** | **%** | **n** | **%** |
| **Number. Of Subjects with AE** | **127** | **46.2%** | **38** | **29.0%** |
| Headache | 15 | 5.5% | 3 | 2.3% |
| Upper Resp Tract Infection | 14 | 5.1% | 5 | 3.8% |
| Diarrhea | 13 | 4.7% | 5 | 3.8% |
| Rash | 8 | 2.9% | 0 | 0.0% |
| Abdominal Pain | 7 | 2.5% | 2 | 1.5% |
| Sinusitis | 6 | 2.2% | 2 | 1.5% |
| Chest Pain | 5 | 1.8% | 2 | 1.5% |
| Gastric Ulcer | 5 | 1.8% | 0 | 0.0% |
| Infection Viral | 5 | 1.8% | 0 | 0.0% |
| Appetite Increased | 4 | 1.5% | 0 | 0.0% |

[a] Trial Merck #010

[b] Omeprazole treatment includes 20 mg.

The AEs are sorted by the omeprazole column.

### 7.2.3 Subgroup Assessment — All Trials (Controlled and Uncontrolled)

Subgroup assessment did not reveal any clinically important differences in AE reporting across age, race, and or gender (data not shown).

### 7.2.4 Adverse Events by Dose — All Trials (Controlled and Uncontrolled)

Proportionately more subjects in open-label trials reported AEs than did subjects participating in double-blind, controlled trials (non-US short-term trials; Table 7.12).

In blinded trial groups (Table 7.12), the proportion of subjects taking Ome 40 mg (25%, N=456) with AEs was not greater than for those treated with Ome 10 mg (31%, N=1364), or those taking Ome 20 mg (27%, N=2113). A dose relationship in regard to AE reporting is not observed in the controlled trials. Likewise, the rate of AE reporting did not increase significantly when the dose was doubled in the open-label studies.

The US short-term trial data by dose also does not show a dose relationship with regard to AE reporting (Table 7.13).

**TABLE 7.12**
**OME RX MOST COMMON ADVERSE EVENTS BY DOSE**
**NON-US GERD/EROSIVE ESOPHAGITIS/DYSPEPSIA PATIENTS**
**SHORT TERM (≤12 WEEKS) CONTROLLED AND UNCONTROLLED TRIALS**
**GROUP 3**



| **DRUG:** | **OME RX [a]** | **Ome Rx [b]** | **OME RX [c]** | **OME RX [d]** | **OME RX [e]** | **OME RX [f]** |
|---|---|---|---|---|---|---|
| **DOSAGE:** | **10 - 40 MG DAILY** | **10 MG DAILY** | **20 MG DAILY** | **20 MG DAILY OPEN** | **40 MG DAILY** | **20/40 MG DAILY BLIND/OPEN** |
| **NO. OF PATIENTS:** | **(N=4671)** | **(N=1364)** | **(N=2113)** | **(N=1014)** | **(N=456)** | **(N=426)** |
| **NO. OF PATIENTS WITH AE (%):** | **1532 (32.8)** | **419 (30.7)** | **567 (26.8)** | **403 (39.7)** | **116 (25.4)** | **179 (42.0)** |
| Diarrhea | 197 (4.2) | 51 (3.7) | 67 (3.2) | 53 (5.2) | 18 (3.9) | 22 (5.2) |
| Headache | 160 (3.4) | 52 (3.8) | 75 (3.5) | 32 (3.2) | 9 (2.0) | 6 (1.4) |
| Respiratory infection | 110 (2.4) | 44 (3.2) | 37 (1.8) | 38 (3.7) | 2 (0.4) | 3 (0.7) |
| Abdominal pain | 94 (2.0) | 25 (1.8) | 31 (1.5) | 21 (2.1) | 11 (2.4) | 12 (2.8) |
| Nausea/nausea (aggravated) | 92 (2.0) | 27 (2.0) | 35 (1.7) | 16 (1.6) | 4 (0.9) | 13 (3.1) |

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-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0007, SH-OMD-0008

c I-606, I-608A, I-609A, I-609B, I-619, I-621A, I-627A, I-640A, I-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0007, SH-OMD-0008

d I-1601A, I-1602A, I-1603

e I-603, I-605A, I-609A, I-609B, I-613A, I-640A, SH-OMD-0003

f I-641A

Adverse events experienced by at least 1.0% of the patients in omeprazole total column are given. The adverse events are sorted by the omeprazole total column.

**TABLE 7.12 (CONTINUED)**
**OME RX MOST COMMON ADVERSE EVENTS BY DOSE**
**NON-US GERD/EROSIVE ESOPHAGITIS/DYSPEPSIA PATIENTS**
**SHORT TERM (≤12 WEEKS) CONTROLLED AND UNCONTROLLED TRIALS**
**GROUP 3**

**(PAGE 2 OF 3)**

| DRUG: | OME RX [a] | Ome Rx [b] | OME RX [c] | OME RX [d] | OME RX [e] | OME RX [f] |
|---|---|---|---|---|---|---|
| **DOSAGE:** | **10 - 40 MG DAILY** | **10 MG DAILY** | **20 MG DAILY** | **20 MG DAILY OPEN** | **40 MG DAILY** | **20/40 MG DAILY BLIND/OPEN** |
| **NO. OF PATIENTS:** | **(N=4671)** | **(N=1364)** | **(N=2113)** | **(N=1014)** | **(N=456)** | **(N=426)** |
| **NO. OF PATIENTS WITH AE (%):** | **1532 (32.8)** | **419 (30.7)** | **567 (26.8)** | **403 (39.7)** | **116 (25.4)** | **179 (42.0)** |
| Flatulence | 86 (1.8) | 19 (1.4) | 41 (1.9) | 14 (1.4) | 12 (2.6) | 4 (0.9) |
| Pharyngitis | 78 (1.7) | 17 (1.2) | 33 (1.6) | 27 (2.7) | 1 (0.2) | 5 (1.2) |
| Constipation | 77 (1.6) | 23 (1.7) | 20 (0.9) | 29 (2.9) | 9 (2.0) | 6 (1.4) |
| Dizziness/vertigo | 76 (1.6) | 24 (1.8) | 27 (1.3) | 8 (0.8) | 10 (2.2) | 7 (1.6) |
| Vomiting | 59 (1.3) | 12 (0.9) | 20 (0.9) | 10 (1.0) | 10 (2.2) | 6 (1.4) |
| Back pain | 54 (1.2) | 18 (1.3) | 19 (0.9) | 21 (2.1) | 1 (0.2) | 4 (0.9) |

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-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0007, SH-OMD-0008

c I-606, I-608A, I-609A, I-609B, I-619, I-621A, I-627A, I-640A, I-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0007, SH-OMD-0008

d I-1601A, I-1602A, I-1603

e I-603, I-605A, I-609A, I-609B, I-613A, I-640A, SH-OMD-0003

f I-641A

Adverse events experienced by at least 1.0% of the patients in omeprazole total column are given. The adverse events are sorted by the omeprazole total column.

**TABLE 7.12 (CONTINUED)**
**OME RX MOST COMMON ADVERSE EVENTS BY DOSE**
**NON-US GERD/EROSIVE ESOPHAGITIS/DYSPEPSIA PATIENTS**
**SHORT TERM (≤12 WEEKS) CONTROLLED AND UNCONTROLLED TRIALS**
**GROUP 3**



| **DRUG:** | **OME RX [a]** | **Ome Rx [b]** | **OME RX [c]** | **OME RX [d]** | **OME RX [e]** | **OME RX [f]** |
|---|---|---|---|---|---|---|
| **DOSAGE:** | **10 - 40 MG DAILY** | **10 MG DAILY** | **20 MG DAILY** | **20 MG DAILY OPEN** | **40 MG DAILY** | **20/40 MG DAILY BLIND/OPEN** |
| **NO. OF PATIENTS:** | **(N=4671)** | **(N=1364)** | **(N=2113)** | **(N=1014)** | **(N=456)** | **(N=426)** |
| **NO. OF PATIENTS WITH AE (%):** | **1532 (32.8)** | **419 (30.7)** | **567 (26.8)** | **403 (39.7)** | **116 (25.4)** | **179 (42.0)** |
| Infection viral | 49 (1.0) | 15 (1.1) | 14 (0.7) | 13 (1.3) | 3 (0.7) | 3 (0.7) |
| Epigastric pain/epigastric pain aggravated | 47 (1.0) | 6 (0.4) | 8 (0.4) | 4 (0.4) | 5 (1.1) | 25 (5.9) |

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-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0007, SH-OMD-0008

c I-606, I-608A, I-609A, I-609B, I-619, I-621A, I-627A, I-640A, I-1601A, I-1602A, I-1603, SH-OMD-0001, SH-OMD-0007, SH-OMD-0008

d I-1601A, I-1602A, I-1603

e I-603, I-605A, I-609A, I-609B, I-613A, I-640A, SH-OMD-0003

f I-641A

Adverse events experienced by at least 1.0% of the patients in omeprazole total column are given. The adverse events are sorted by the omeprazole total column.

**TABLE 7.13**
**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 | 3.7 | 8 | 1.4 |
| SINUSITIS | 1 | 0.8 | 18 | 4.7 | 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 GLUTAMIC-OXALOACETIC TA INC | 3 | 2.3 | 2 | 0.5 | 0 | 0.0 |
| SERUM GLUTAMIC-PYRUVIC TA INCR | 3 | 2.3 | 2 | 0.5 | 0 | 0.0 |
| CRAMP ABDOMINAL | 3 | 2.3 | 1 | 0.3 | 0 | 0.0 |

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 7.13 (CONTINUED)**
**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] |
| HAEMATURIA | 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 |

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 7.13 (CONTINUED)**
**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**

**(PAGE 3 OF 3)**

| 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] |
| 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.

### 7.2.5 Patients who Discontinued Study Drug During Clinical Trials Due to an Adverse Event — All Trials (Controlled and Uncontrolled)

Omeprazole-treated patients did not discontinue the study drug during Rx trials at rates greater than placebo-treated patients across all groupings of trials (data not shown). The highest percentage of patients in an Ome group who discontinued the study drug due to an AE occurred in the non-US long-term trials at 3.7%.

### 7.2.6 Deaths and Other Serious Adverse Events — All GERD, EE, and Dyspepsia Trials (Controlled and Uncontrolled)

Table 7.14 presents a summary of the 10 fatal SAEs (deaths) in all US and non-US short- and long-term trials. Four deaths occurred in Ome-treated patients in the short-term non-US clinical trials. Upon review, all cases involved significant concurrent underlying medical conditions that predated the use of Ome and that were the most likely causative factor in the patient's death. No deaths were reported for patients in the US short-term trials. There were

5 deaths in non-US long-term trials. As was true with the short-term trials, the deaths were attributable to a pre-existing medical condition, rather than to the administration of Ome. The remaining fatality occurred in the only US long-term trial. A patient experienced chest pain and study medication was discontinued. Follow-up information noted a diagnosis of lung cancer with extensive metastases. It was reported that the patient subsequently died. The fatal event was determined as probably not related to Ome.

In the non-US short term trials 45 subjects reported 49 non fatal SAEs. Three of the cases (0.1%) included a SAE considered related to the Ome treatment and in the remaining 42 cases the events were considered unrelated. The most commonly reported SAE with Ome use was angina pectoris.

In the US short-term trials, a total of 20 subjects (1.9%) reported 56 non-fatal SAEs. The most commonly reported SAEs with Ome use were nausea and vomiting.

In long-term $R_x$ Ome non-US clinical trials, 2 subjects (0.2%) reported 2 non-fatal SAEs (syncope and atrial fibrillation) which were considered related to the Ome treatment, and 49 subjects (0.9%) reported 59 non-fatal SAEs not related to Ome. The most common SAE with Ome use was angina pectoris.

In the US long-term trial, a total of 13 subjects (4.7%) reported 20 SAEs. The most common SAEs were cholelithiasis and pulmonary carcinoma.

For all these studies, the percentages of SAEs in Ome-treated groups were comparable to those in the placebo-treated groups.

### 7.2.7 Deaths and Other Serious Adverse Events — Studies from Other Indications

From additional worldwide studies that include Astra trials, Compassionate Use Trials, non-sponsored trials, and reports of trials in the published literature, there are reports of other SAEs and deaths during the use of orally administered Ome. The most commonly reported causes of death were myocardial infarction, carcinoma, and pneumonia. Many of the patients who died were elderly and had a serious medical illness prior to entering the study, and in most cases, this pre-existing severe illness was listed as the cause of death.

**TABLE 7.14**
**OME RX FATAL SERIOUS ADVERSE EVENTS**
**NON-US AND US GERD/EE/DYSPEPSIA PATIENTS**
**SHORT-TERM AND LONG-TERM CONTROLLED AND UNCONTROLLED TRIALS**

| Patient | Trial Type | Dose Level | Gender | Age | Known Medical Conditions | Known Concomitant Medications | Cause of Death | Relationship to Study Medication |
|---|---|---|---|---|---|---|---|---|
| 1-603-212 | Short-Term Non-US | 40 mg/ day Ome | M | 79 | Reflux Esophagitis<br>Adenocarcinoma of the Colon | | Embolism | Not Assessed |
| 1-606-0434 | Short-Term Non-US | 20 mg/ day Ome | F | 75 | Reflux Esophagitis<br>Chronic Diarrhea, Proctitis | | Pneumonia<br>Sepsis | Unlikely |
| 1-640-01204 | Short-Term Non-US | 20 mg/ day Ome | M | 78 | Diabetes Mellitus<br>Thrombosis Cerebri<br>Aphasia, Hemiparesis | | Brain Neoplasm Malignant | Unlikely |
| SH-OMD-0007-012-0201 | Short-Term Non-US | 20 mg/ day Ome | F | 61 | Dyspepsia<br>Severe Back Pain | | Pulmonary Carcinoma | Unlikely |
| 1-621-435/427 | Long-Term Non-US | 20 mg/ day Ome | M | 69 | Reflux Esophagitis | | Embolism Pulmonary | Not Assessed |
| 1-640-01227/594 | Long-Term Non-US | 20 mg/ day Ome | M | 63 | Alcoholic Cirrhosis<br>Hypertension<br>Ascites<br>Esophageal Varices<br>Encephalopathy<br>Arthritis<br>Spinal Osteomyelitis | Paracetamol<br>Lactulose<br>Apurin<br>Pursennid<br>Diural | Coma hepatic | Unlikely |
| 1-621-12010/110 | Long-Term Non-US | 10 mg/ day Ome | M | 68 | Heart Failure<br>Pulmonary Edema<br>Arthritis | Spironolactone<br>Digoxin<br>Furix, Zantac | Myocardial Infarction | Unlikely |
| 1-641-12023/123 | Long-Term Non-US | 10 mg/ day Ome | F | 73 | Esophagitis | | Myocardial Infarction | Unlikely |
| 1-641-22010/108 | Long-Term Non-US | 10 mg/ day Ome | M | 63 | Esophagitis<br>Peritonitis<br>Ileus | | Intestinal Perforation | Unlikely |
| 010-1488 | Short/Long -Term US | 20 mg/ day Ome | M | 69 | Chest Pain<br>Lung Neoplasm, Malignant<br>Death | NA | Cancer | Probably not |

## 7.3 Summary: OTC versus Prescription Omeprazole Safety

A total of 11 US OTC Ome-Mg studies involving 11,790 subjects and 35 US and non-US Rx Ome studies involving over 7500 subjects are included in this safety analysis. These studies involve 8670 subjects who took Ome-Mg (5040 on Ome-Mg 20, 3630 on Ome-Mg 10) and 5757 unique subjects who have taken Rx Ome. The demographics for the Ome-Mg vs. the Rx Ome groups were comparable.

A comprehensive review of AEs for both Ome-treated populations revealed that the most commonly reported AEs were comparable between Ome-Mg and Rx Ome and included headache, infection, and diarrhea. There was no apparent dose-dependent increase in AE reporting for Ome-treated subjects during all these studies. In long-term trials the safety profile of Ome did not demonstrate increases in the number of AEs disproportionate to the duration of treatment. In all these clinical studies, Ome-Mg, as well as Rx Ome, had a safety profile comparable to placebo.

No gender-dependent increases in AE reporting were found. No age-dependent increases in AE reporting were found except for a higher AE reporting incidence in the age group 12–17 in Ome-Mg OTC trial 067, which was an open-label trial.

The percentage of subjects reporting one or more AEs was greater for Ome-Mg 10 and Ome-Mg 20-treated subjects participating in uncontrolled clinical trials (28% to 31%) compared to Ome-Mg 10 and 20-treated subjects in controlled clinical trials (15% - 15%), which can again be attributed to the fact that the studies were open-label and lasted longer than the controlled trials. The same is true for the Rx trials.

In the controlled short-term non US Ome Rx trials, 29% of patients reported one or more AEs compared to 49% in the US trials. Many of the AEs in that group of US trials were cold and flu type symptoms also seen in the comparator and placebo groups.

The percentage of Ome-Mg 20-treated subjects reporting 1 or more AEs did not increase with either increased duration of dosing or increased number of tablets used, nor was there an increase in the reporting of any individual AEs.

The percentage of discontinuations due to AEs was small (0.5%) in Ome-Mg clinical trials. The greatest percentage of Rx Ome-treated subjects discontinuing study drug treatment due to an AE occurred in the non-US long-term trial (3.7%). In all these studies, the percentage of Ome-treated subject discontinuations due to AEs was comparable or smaller compared to placebo-treated subjects.

Two Ome-Mg-treated subjects (Ome-Mg 10 and 20) died, but the deaths were considered unlikely to be due to study medication (one was judged to be an overdose). There were nine fatal cases in $R_x$ Ome non-US clinical trials and one death in a US clinical trial. All these deaths involved significant concurrent medical conditions that were most likely the causative factor of these fatalities.

A total of 31 subjects reported SAEs during the OTC clinical trials, with an incidence of 0.4% for Ome-Mg 10-treated subjects, 0.2% for Ome-Mg 20-treated subjects, and 0.1% for placebo-treated subjects. In one case, the Ome treatment was considered probably related to the event (serum sickness). In short-term non-US $R_x$ Ome clinical trials, 3 SAEs (0.1%) (Arthralgia/Enterocolitis, Bronchospasm, Interstitial Nephritis) were considered related to the Ome treatment, and 42 SAEs (0.9%) were not related to the Ome treatment.

In the non-US short term trials 45 subjects reported 49 non-fatal SAEs. Three of the cases (0.1%) included a SAE considered related to the Ome treatment and in the remaining 42 cases the events were considered unrelated. In the US short-term trials, a total of 20 subjects (1.9%) reported 56 non-fatal SAEs. In long-term $R_x$ Ome non-US clinical trials, 2 subjects (0.2%) reported 2 non-fatal SAEs (syncope and atrial fibrillation) which were considered related to the Ome treatment, and 49 subjects (0.9%) reported 59 non-fatal SAEs not related to Ome. In the US long-term trial, a total of 13 subjects (4.7%) reported 20 non-fatal SAEs. For all these studies, the percentages of SAEs in Ome-treated groups were comparable to those in the placebo-treated groups.

Overall, an evaluation of the safety data generated from subjects treated with Ome-Mg, or $R_x$ Ome demonstrated that safety profiles of these treatment forms are comparable.

## 7.4 Overall Safety Conclusion from Clinical Trials

In summary, the clinical trial safety databases include over 14,000 subjects/patients who took either Ome capsules or Ome magnesium tablets in either Rx trials or OTC clinical trials. Additional safety data are included from approximately 5,000 patients/subjects treated with placebo or an active comparator.

The totality of these data indicate that in the double blind, placebo-controlled trials

1. The safety profile for Ome-Mg-treated patients was comparable to that for Rx Ome and placebo.

2. There was no dose-related increase in AE reporting for Ome-Mg-treated patients during the clinical studies.

3. AEs reported by Ome-Mg-treated patients were well characterized and benign.

4. These data provide strong evidence regarding the safety of both the 10 mg and 20 mg Ome-Mg dosages for OTC use.

## 7.5 Prescription Omeprazole Post-Marketing Surveillance Data

AstraZeneca LP maintains a worldwide database (SafeTNet) of domestic and foreign serious, and domestic non-serious, post-marketing AEs received from various countries in which Ome has been marketed.

For purposes of this briefing document, the SafeTNet database was searched for reports received and verified on or before 30-Jun-98 in which oral Ome was the suspected medication associated with the report. This experience encompasses approximately 300 million courses of Ome patient treatments worldwide with approximately 90 million in the US. A single patient treatment is defined as a total Rx. A total of 7,344 cases were retrieved which included 15,385 AEs.

Table 7.15 displays number of courses of therapy, in millions, for each 2 year interval from 1990 through mid-1998. This totals approximately 300 million courses of therapy over a 10 years; the number of reports of serious adverse events in each 2 year interval, and the incidence per one million exposures. There has been no increase of the reporting rate of serious adverse events over time.

**TABLE 7.15**
**WORLDWIDE SERIOUS POST-MARKETING ADVERSE EVENTS**
**SAE INCIDENCE BY RX SALES (IN MILLIONS)**
**REPORTED IN 2-YEAR INTERVALS (1990–6/98)***

| Period | 90–91 | 92–93 | 94–95 | 96–97 | 1/98–6/98 |
|---|---|---|---|---|---|
| **Rx (in millions)** | 22.7 | 52.3 | 74.3 | 100.4 | 43.5 |
| **SAEs** | 457 | 739 | 1168 | 1113 | 361 |
| **Incidence / Million Rx** | 20.1 | 14.1 | 15.7 | 11.1 | 8.3 |

* Number of serious adverse event (SAE) reports calculated from safety database frozen and locked on 30-Jun-98.

### 7.5.1 All Worldwide Serious Adverse Events and US Non-Serious Adverse Events

The ten most frequently reported SAEs, from post-marketing experience with Ome, listed in decreasing order of frequency, are presented in Table 7.16.

**TABLE 7.16**
**WORLDWIDE SERIOUS POST-MARKETING REPORTS**
**DESCENDING FREQUENCY FOR TOP 50 TERMS**
**ASTRAZENECA LP SAFETNET DATABASE**

| ADVERSE EVENT | PATIENT COUNT |
|---|---|
| THROMBOCYTOPENIA | 108 |
| HEPATITIS | 64 |
| NEPHRITIS INTERSTITIAL | 57 |
| FEVER | 54 |
| INTERACTION | 53 |
| PANCYTOPENIA | 50 |
| CONFUSION | 49 |
| PANCREATITIS | 46 |
| HYPONATRAEMIA | 45 |
| VOMITING | 44 |

Patient Count = Number of patients who reported the specified adverse event

The ten most frequently reported SAEs, from post-marketing experience with Ome, listed in decreasing order of frequency, with incidence per million exposures in the first 5 years and the second 5 years are presented in Table 7.17.

**TABLE 7.17**
**TEN MOST FREQUENT WORLDWIDE SERIOUS POST-MARKETING ADVERSE EVENTS**
**SAE INCIDENCE BY RX SALES (IN MILLIONS)**
**REPORTED IN 4-YEAR INTERVALS (1990–6/98)***

| | Incidence / Million | |
|---|---|---|
| **Reported Term (SAE)** | **90 - 94** | **95 – 6/98** |
| **Thrombocytopenia** | 0.4 | 0.3 |
| **Hepatitis** | 0.2 | 0.2 |
| **Interstitial Nephritis** | 0.2 | 0.2 |
| **Fever** | 0.3 | 0.1 |
| **Interaction** | 0.3 | 0.1 |
| **Pancytopenia** | 0.2 | 0.1 |
| **Confusion** | 0.1 | 0.2 |
| **Pancreatitis** | 0.1 | 0.2 |
| **Hyponatremia** | 0.1 | 0.2 |
| **Vomiting** | 0.2 | 0.1 |

* Number of serious adverse event (SAE) reports calculated from safety database frozen and locked on 30-Jun-98.

### 7.5.2 Worldwide Serious Fatal Adverse Events

There were a total of 287 deaths, 145 of which were coded as deaths (142) or sudden death (3) and an additional 142 cases in which death was an outcome but was not coded as an AE. The most commonly reported fatal SAE terms are myocardial infarction, sepsis, cardiac arrest, hepatic failure, and cardiac failure. The common theme in these cases is that multiple causative factors were present that could have resulted in the death of the patient. A review of these cases suggests no clinically meaningful trend exists to establish a cause-and-effect relationship between Ome intake and an outcome of death.

### 7.5.3 Worldwide Serious Non-Fatal Adverse Events

A total of 1,750 patients experienced an SAE not resulting in death. The most frequent non-fatal SAEs reported were thrombocytopenia, hepatitis, interstitial nephritis, fever, and drug interaction.

### 7.5.4 Worldwide Serious and US Non Serious Adverse Events for Children

A total of 98 patients less than 12-years-old reported an AE. The most common AEs noted were Body as a Whole—General Disorder Not Otherwise Specified (includes 27 cases of off-label pediatric use with no AE identified) and drug maladministration. There was one neonatal case with an outcome of death:

A 28-year-old insulin-dependent, diabetic, pregnant female (approximately 18 weeks gestation) was placed on Ome therapy for symptoms thought to be related to GERD. Ultrasound at that time was normal. Concomitant medications included insulin, sucralfate, metoclopramide and docusate sodium-casanthranol. Subsequent ultrasounds (at approximately 21 and 29 weeks) showed abnormal posturing of the extremities, hydrocephalus, and severe microcephaly. Ome therapy was discontinued at 31 to 32 weeks gestation. Labor was induced at 39 weeks. A male infant weighing 2890 grams with abnormalities including microencephaly, bilateral clubbing of feet, abnormal lower extremities consisting of contracture and hyperextension of the knees bilaterally was delivered. The baby died two weeks later. CT scan findings were felt to be consistent with hydranencephaly (the cerebral cortex was visualized on prenatal ultrasounds). The reporting physician noted "the malformations appeared to develop on prenatal ultrasound in the same time sequence that Ome was used".

A total of 92 AEs were experienced by 39 patients aged 12–16 years. The most common AE noted was Body as a Whole — General Disorder Not Otherwise Specified. There was one case with an outcome of death:

A 13-year-old female patient with a prior history of serious medical illness including renal insufficiencies and autoimmune hepatitis developed aplastic anemia (no lab results were reported) after approximately one year on Ome therapy. The patient was also reportedly taking azathioprine, amitriptyline HCL, prednisone, bactrim, ursodeoxycholic acid, enalapril maleate, eopetin alfa, amlodipine besilate and losartan potassium. Therapy with Ome was withdrawn; the patient recovered. The patient later died (date note reported) from renal insufficiency. The reporting physician felt Ome therapy was not related to the patient's death.

### 7.5.5 Worldwide Serious and US Non Serious Adverse Events for Adults ≥ 65 Years of Age

A total of 4,722 AEs were experienced by 2,050 subjects ≥65 years of age. The most commonly reported AEs were diarrhea, nausea, rash, headache, and dizziness.

## 7.6 Safety Conclusions

A review of OTC and Rx AE data has not shown any significant issues or patterns which would prevent Ome-Mg from being used safely in an OTC setting; both Ome and Ome-Mg show similar safety profiles to placebo, as well as to currently available OTC heartburn medications.[33] The most common AEs are transient, not serious, and easily resolved. Omeprazole magnesium is suitable for use in a general heartburn population.

With 300 million estimated Ome patient treatments worldwide available information suggests that Ome has a very favorable safety profile which is comparable for patients of all ages. The most common AEs were consistent with current labeling and with clinical study experience.