

ORIGINAL ARTICLE

Comparison of Prilosec OTC™ (omeprazole magnesium 20·6 mg) to placebo for 14 days in the treatment of frequent heartburn

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SUMMARY

Purpose: Consumer surveys have identified an over-the-counter (OTC) medication that provides complete and long-lasting relief of frequent heartburn as an unmet consumer need. The purpose of the two identical studies reported in this paper was to evaluate the safety and effectiveness of 10·3 and 20·6 mg omeprazole magnesium, referred to as Ome-Mg 10 and Ome-Mg 20, respectively (equivalent to 10 and 20 mg omeprazole) for the treatment of frequent heartburn administered as a novel 14-day OTC regimen.

Subjects and Methods: Subjects with frequent heartburn (heartburn two or more days per week) took Ome-Mg 10, Ome-Mg 20, or placebo for 14 consecutive mornings. Statistical analyses compared percentage of subjects with no heartburn 24 h after the first dose, after the last dose (day 14), and percentage of days that subjects were heartburn-free. Nocturnal heartburn and heartburn rated no more than mild were also assessed.

Results: Twenty-four hours following the first dose, nearly 50% of subjects receiving Ome-Mg 20 reported no heartburn, and more than 80% receiving Ome-Mg 20 had no more than mild heartburn. Both doses were significantly more effective than placebo on days 1 and 14 for percentage of subjects heartburn-free for 24 h ($P \leq 0\cdot003$), and across all 14 days for percentage of heartburn-free days ($P < 0\cdot001$). Ome-Mg 20 was significantly more effective than placebo in

preventing nocturnal heartburn across all 14 days ($P < 0\cdot001$). Ome-Mg was well tolerated.

Conclusion: These trials demonstrated the safety and effectiveness of a novel 14-day regimen of Ome-Mg 20 in completely preventing heartburn for 24 h establishing it as an excellent self-care treatment for frequent heartburn and supporting the approval of Prilosec OTC™.

Keywords: gastroesophageal reflux, heartburn, omeprazole, self-medication

INTRODUCTION

Heartburn is a common complaint, with 44–60% of adults in the United States reporting heartburn at least once a month (1). A recent Gallup poll showed that of those with heartburn, 45% (approximately 40 million adults in the US) report frequent symptoms, two or more days per week (2). Although the majority of adults with frequent heartburn have seen a healthcare provider (3), they primarily rely on over-the-counter (OTC) heartburn remedies to manage their symptoms. Those individuals who choose to manage frequent heartburn with OTC heartburn preparations generally mix medications to completely control symptoms. Still, consumer surveys show that a significant proportion of individuals with frequent heartburn remain dissatisfied with available OTC products, primarily because the medications do not provide complete or long-lasting relief from symptoms (4). A more recent survey conducted by the National Heartburn Alliance also found that frequent heartburn sufferers report significant effects of symptoms on their quality of life: more than 60% mention that heartburn interrupts their sleep, and more than 30% note decrease in job

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performance because of heartburn (5). Clearly, an effective OTC therapy for frequent heartburn has been an ongoing unmet consumer need.

As a result of the long-term safety and proven efficacy of omeprazole (Prilosec[®], AstraZeneca LP, Wilmington, DE, USA by Merck & Co., Whitehouse Station, NJ, USA) for the treatment of acid reflux-related symptoms, it was identified as a logical and appropriate self-care therapy for frequent heartburn. Omeprazole magnesium, at the prescription dose of 20 mg (Prilosec OTC[™]), received approval in June 2003 as an effective OTC therapy for frequent heartburn.

The purpose of the two identical studies reported in this paper was to evaluate the safety and effectiveness of Ome-Mg 10 and Ome-Mg 20 for the treatment of frequent heartburn administered as a novel 14-day regimen intended for the OTC setting.

METHODS

Study design and sample recruitment

Two studies, multicentre, double-blind, randomized, double-dummy, parallel, placebo-controlled, and identical with respect to design, conduct and data analysis, were carried out in 49 US primary care study sites. Collectively, 3162 subjects were randomized to treatment: 2109 to Ome-Mg and 1053 to placebo. The studies involved a 1-week, single-blind, placebo run-in phase and a 2-week, double-blind, treatment phase during which eligible subjects [those with heartburn two or more days per week of the run-in period with a history of symptomatic relief with antacids or OTC histamine₂-receptor antagonists (H₂RAs) and who did not have a previous physician diagnosis of GERD] were randomized to receive a single daily (morning) dose of Ome-Mg 20, Ome-Mg 10, or placebo every day for 14 consecutive days. Each morning subjects recorded in a diary whether or not heartburn was present during the previous 24-h period and, if present, the most severe episode of heartburn, using an internally validated four-point scale, where 0 = no heartburn, 1 = mild heartburn present but easily tolerated, 2 = moderate heartburn sufficient to cause interference with normal activities or sleep, and 3 = severe heartburn incapacitating and subject is unable to perform normal daily activities or sleep.

Outcomes measured and statistical methods

The primary efficacy variable was no heartburn over the previous 24 h (i.e. complete prevention of heartburn for a full day, or heartburn-free for 24 h). Efficacy was evaluated following the first dose of medication, following the last dose of medication and over the entire 14 days of the treatment phase. Secondary efficacy variables included no nocturnal heartburn and no more than mild heartburn. For both studies, a Cochran–Mantel–Haenszel test statistic was used to compare treatment effects on day 1 for heartburn-free over 24 h, no nocturnal heartburn and no more than mild heartburn over 24 h. A logistic regression analysis was used to compute odds ratios for each treatment comparison and to assess treatment-by-centre interaction for day 1 variables. For each endpoint, an ANOVA was performed on each of the three variables to compare treatments with regard to mean percent of days over the 2-week treatment phase when an event took place. Generalized Estimating Equations (GEE) were used to assess the same three variables over repeated doses. The statistical software used was SAS[®] version 6.12 (SAS Institute Inc., Cary, NC, USA) under UNIX[™].

RESULTS

Study sample

A total of 3557 subjects entered the run-in phase. Of these, 3162 subjects met the inclusion criteria and were randomized to treatment and 3124 subjects were included in the intent-to-treat (ITT) data set for statistical analysis: 2085 received active medication (1047 Ome-Mg 20) and 1039 placebo. Table 1 provides a summary of demographic and heartburn baseline characteristics by study medication group and trial. Baseline characteristics were similar across treatment groups and trials. The mean reported baseline heartburn frequency was 5 days per week and severity was mild-to-moderate.

Heartburn-free day 1 results

Table 2 displays results for the primary efficacy parameter, heartburn-free for 24 h, for day 1 after the first single morning dose. In both studies, a significantly greater percentage of subjects in the Ome-Mg 10 and Ome-Mg 20 treatment groups

Table 1. Demographic and other baseline characteristics

	Trial 1			Trial 2		
	Ome-Mg 20 (n = 523)	Ome-Mg 10 (n = 518)	Placebo (n = 519)	Ome-Mg 20 (n = 524)	Ome-Mg 10 (n = 520)	Placebo (n = 520)
Gender						
Female	297 (56.8)	284 (54.8)	287 (55.3)	283 (54.0)	287 (55.2)	293 (56.3)
Male	226 (43.2)	234 (45.2)	232 (44.7)	241 (46.0)	233 (44.8)	227 (43.7)
Race						
Asian	4 (0.8)	7 (1.4)	7 (1.3)	1 (0.2)	2 (0.4)	4 (0.8)
Black people	63 (12.0)	55 (10.6)	57 (11.0)	32 (6.1)	31 (6.0)	33 (6.3)
White people	401 (76.7)	410 (79.0)	399 (76.9)	443 (84.5)	450 (86.5)	445 (85.6)
Hispanic	48 (9.2)	41 (7.9)	51 (9.8)	36 (6.9)	29 (5.6)	33 (6.3)
Other	7 (1.3)	6 (1.2)	5 (1.0)	12 (2.3)	8 (1.5)	5 (1.0)
Age (years)						
Mean (SD)	44.5 (12.8)	44.1 (13.0)	43.7 (13.2)	46.7 (14.2)	47.3 (14.7)	46.0 (14.1)
Min-max	18-86	19-86	18-79	20-84	18-84	18-79
Average heartburn severity (0-3 scale reported during run-in)						
Mean (SD)	1.5 (0.42)	1.5 (0.41)	1.5 (0.42)	1.6 (0.43)	1.5 (0.39)	1.5 (0.41)
Heartburn frequency (% of days during run-in)						
Mean (SD)	74.3 (24.4)	73.7 (24.1)	75.2 (24.2)	74.2 (23.6)	74.3 (24.6)	74.2 (24.2)
≥50%	419 (80.1)	424 (81.9)	422 (81.3)	426 (81.3)	414 (79.6)	417 (80.2)

Values are given as *n* (%) of intent-to-treat subjects in each treatment group, unless otherwise stated.

were heartburn-free than in the placebo group ($P \leq 0.003$). In study 1, 49.7% of subjects receiving Ome-Mg 20 and 41.5% of subjects receiving Ome-Mg 10 were heartburn-free for the full day after the first dose, whereas in study 2, 46.8% of subjects receiving Ome-Mg 20 and 45.2% of subjects receiving Ome-Mg 10 were heartburn-free for the full day after the first dose. In study 1, Ome-Mg 20 had a significantly higher percentage of heartburn-free subjects than Ome-Mg 10 ($P = 0.008$).

Heartburn-free day 14 results

In both studies, a significantly greater percentage of subjects receiving Ome-Mg 10 and Ome-Mg 20 were heartburn-free on day 14 compared with placebo ($P < 0.001$). In study 1, 69.7% receiving Ome-Mg 20, 71.7% receiving Ome-Mg 10 and 42.7% receiving placebo did not experience heartburn on day 14, whereas in study 2, the corresponding results were 73.0, 66.4 and 43.0% for Ome-Mg 20, Ome-Mg 10 and placebo respectively. In study 2, Ome-Mg 20 had a significantly higher percentage of heartburn-free subjects than Ome-Mg 10 ($P = 0.015$).

Heartburn-free results across 14 days of therapy

Figure 1 and Table 3 display results for the primary efficacy parameter, heartburn-free over 24 h, across 14 consecutive days of dosing. Each study shows Ome-Mg 10 and Ome-Mg 20 statistically superior to placebo for percentage of days heartburn-free ($P \leq 0.001$). In study 1, the percentage of days heartburn-free was 64.4% for Ome-Mg 20, 60.8% for Ome-Mg 10 mg and 39.4% for placebo. In study 2, the percentage of days heartburn-free was 67.8% for Ome-Mg 20, 61.4% for Ome-Mg 10 and 37.9% for placebo. Results across 14 days in study 2 showed Ome-Mg 20 statistically more effective than Ome-Mg 10 ($P < 0.001$).

Nocturnal heartburn results

In study 1, the percentage of subjects with no nocturnal heartburn following the first dose was 78.4% for Ome-Mg 20 ($P \leq 0.004$ vs. placebo). In study 2, the percentage of subjects with no nocturnal heartburn following the first dose was 77.7% for Ome-Mg 20, which was not significantly different from placebo ($P = 0.141$). When the data are

Study 1	Ome-Mg 20	Ome-Mg 10	Placebo
Heartburn-free (%)	49.7 (260/523)	41.5 (215/518)	32.6 (169/519)
Comparison	P-value	Odds ratio (95% CI)	Diff in prop. (95% CI)
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 2	Ome-Mg 20	Ome-Mg 10	Placebo
Heartburn-free (%)	46.8 (245/524)	45.2 (235/520)	32.1 (167/520)
Comparison	P-value	Odds ratio (95% CI)	Diff in prop. (95% CI)
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)

Table 2. Analysis of primary efficacy variable no heartburn over 24 h on day 1 (intent-to-treat subjects)

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

Estimated odds ratios and 95% confidence intervals (CI) from logistic regression analysis with treatment and centre (pooled investigators) as categorical variables.

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

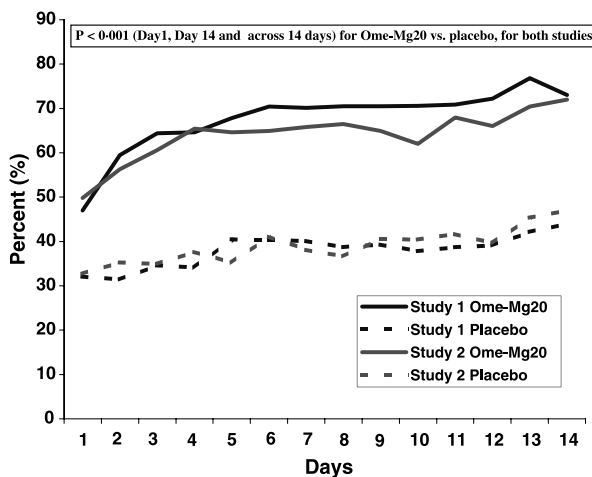


Fig. 1. Percentage of subjects heartburn-free over 14 days of therapy.

evaluated across all 14 days of therapy (Fig. 2), both Ome-Mg 10 and Ome-Mg 20 showed a significantly greater percentage of heartburn-free nights vs. placebo ($P < 0.001$).

Results for 'no more than mild' heartburn

Complete prevention of heartburn or heartburn-free, represents the most rigorous symptom measure that can be applied to a 24-h period. A less rigorous measure, such as 'adequate relief', also defined as heartburn no more than mild, is often utilized in studies of heartburn treatment with OTC medications. For comparison, data are provided for subjects with no more than mild heartburn, defined as heartburn that is present but easily tolerated (Fig. 3). In study 1, the percentage of subjects with no more than mild heartburn following the first dose was 81% for Ome-Mg 20 ($P \leq 0.001$ vs. placebo). Results of study 2 were similar: the percentage of subjects with 'no more than mild heartburn' following the first dose was 81.8% for Ome-Mg 20 mg ($P \leq 0.001$ vs. placebo). Across 14 days of consecutive daily dosing, Ome-Mg 20 subjects reported a significantly greater percentage of days with no more than mild heartburn (88.6% for both studies) vs. placebo ($P < 0.001$). Ome-Mg

Table 3. Analysis of primary efficacy variable no heartburn over 24 h across 14 days (intent-to-treat subjects)

Study 1	Ome-Mg 20	Ome-Mg 10	Placebo
Heartburn-free (mean% days)	64.4%	60.8%	39.4%
Comparison	P-value	Difference in means	95% CI
Ome-Mg 20 vs. placebo	<0.001	25.0	(21.1, 28.8)
Ome-Mg 10 vs. placebo	<0.001	21.4	(17.6, 25.2)
Ome-Mg 20 vs. Ome-Mg 10	0.068	3.6	(-0.3, 7.4)
Study 2	Ome-Mg 20	Ome-Mg 10	Placebo
Heartburn-free (mean% days)	67.8%	61.4%	37.9%
Comparison	P-value	Difference in means	95% CI
Ome-Mg 20 vs. placebo	<0.001	29.8	(26.1, 33.5)
Ome-Mg 10 vs. placebo	<0.001	23.5	(19.7, 27.2)
Ome-Mg 20 vs. Ome-Mg 10	<0.001	6.4	(2.7, 10.1)

P-values are from *t*-test, comparing treatment means (difference in LS means from ANOVA model using treatment and investigator as factors).

Estimated difference in mean% days heartburn-free (difference in LS means from ANOVA model using treatment and investigator as factors).

95% confidence interval (two-sided) for estimated difference in means.

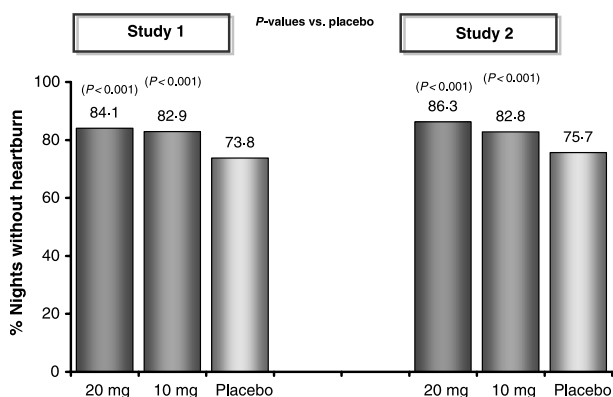


Fig. 2. Percentage of nights with no nocturnal heartburn over 14 days of therapy.

20 and Ome-Mg 10 were not significantly different from each other for percentage of days with no more than mild heartburn, although Ome-Mg 20 was numerically superior to Ome-Mg 10 on day 1 and across all 14 days of the study (Fig. 4).

Safety results

Overall, Ome-Mg was very well tolerated. The most common adverse events across all treatment

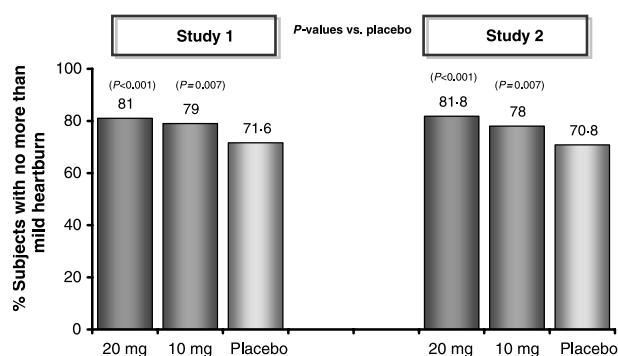


Fig. 3. Percentage of subjects with no more than mild heartburn on day 1.

groups in both studies were very similar. Those reported at incidences of >1% (all below 5%) included diarrhoea, headache, infections/respiratory infections, abdominal pain and nausea/vomiting. Subjects provided serum chemistry and haematology samples at baseline and at the completion of the double-blind treatment phase of the study; all treatment groups were similar with respect to change from baseline for all values and no subject had clinically concerning laboratory

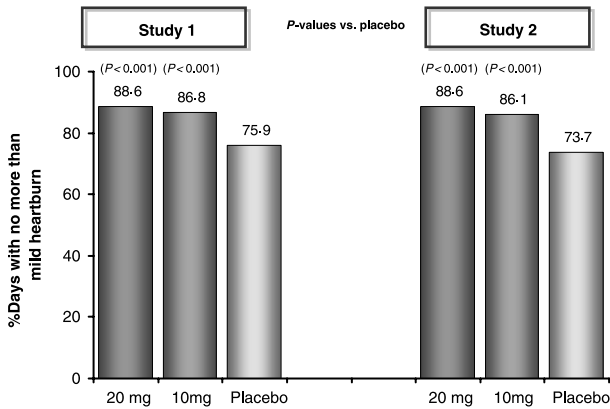


Fig. 4. Percentage of days with no more than mild heartburn.

findings. Overall there were six adverse events classified as serious across both studies (one in the Ome-Mg 20 group, four in the Ome-Mg 10 group and one in the placebo group), and all were considered unlikely to be related to study medication. There were no deaths in either study. The most common adverse events reported in both studies are detailed in Table 4.

DISCUSSION

The two clinical trials reported here confirm that Ome-Mg 20, the medication in Prilosec OTC™, was very effective in eliminating symptoms of frequent heartburn (heartburn two or more days per week) and that 20 mg is the most appropriate OTC dose. Not only was Ome-Mg 20 effective with the first dose, completely preventing heartburn for 24 h but also this efficacy was sustained through the last dose on day 14. Although both Ome-Mg 10 and Ome-Mg 20 were superior to placebo, the 20 mg dose consistently demonstrated a higher level of prevention across all temporal variables, and for several of these variables, 20 mg was statistically superior. In further support of the 20 mg dose, previously published pharmacodynamic data clearly demonstrate more pronounced and consistent gastric acid inhibition for 20 mg (6, 7). Finally, the safety profiles for the two doses were very similar.

This rapid and sustained effect on symptoms is particularly important because, although up to 78% of individuals with frequent heartburn have

Table 4. Most common adverse events ($\geq 1\%$ in any treatment group)

	Trial 1			Trial 2		
	Ome-Mg 20 (n = 528)	Ome-Mg 10 (n = 527)	Placebo (n = 526)	Ome-Mg 20 (n = 525)	Ome-Mg 10 (n = 526)	Placebo (n = 525)
<i>COSTART term</i>						
Infection	12 (2.3)	12 (2.3)	17 (3.0)	12 (2.3)	14 (2.7)	14 (2.7)
Diarrhea	16 (3.0)	13 (2.5)	8 (1.5)	9 (1.7)	14 (2.7)	11 (2.1)
Headache	10 (1.9)	9 (1.7)	14 (2.7)	16 (3.0)	10 (1.9)	10 (1.9)
Abdominal Pain	8 (1.5)	2 (0.4)	5 (1.0)	8 (1.5)	1 (0.2)	10 (1.9)
Flu Symptoms	6 (1.1)	6 (1.1)	2 (0.4)	5 (1.0)	2 (0.4)	5 (1.0)
Nausea	2 (0.4)	5 (0.9)	5 (1.0)	11 (2.1)	11 (2.1)	5 (1.0)
Rhinitis	2 (0.4)	1 (0.2)	5 (1.0)	5 (1.0)	2 (0.4)	1 (0.2)
Flatulence ^a	–	–	–	5 (1.0)	2 (0.4)	6 (1.1)
Pharyngitis ^a	–	–	–	5 (1.0)	7 (1.3)	1 (0.2)
Constipation ^a	–	–	–	7 (1.3)	3 (0.6)	2 (0.4)
Vomiting ^a	–	–	–	5 (1.0)	2 (0.4)	4 (0.8)
Dyspepsia ^a	–	–	–	5 (1.0)	1 (0.2)	1 (0.2)

n, number of subjects who took at least one dose of study medication.

Values are given as n (%), number of subjects and percentage of subjects (with respect to n) with adverse event within specified COSTART term.

^aAdverse event not reported in $\geq 1\%$ in any trial 1 treatment group.

seen a healthcare provider (2, 4), they still rely on OTC heartburn remedies. A significant portion of them are dissatisfied with current OTC products, primarily because these medications do not provide sustained symptom relief (4, 5). Those OTC products that are intended to treat or prevent episodic occasional heartburn (antacids, H₂RAs) do not provide the degree of ongoing acid control needed for the treatment of frequent heartburn. While antacids quickly neutralize acid, providing immediate relief of existing heartburn, their duration of action is rather short – minutes to several hours – which leads to prompt return of symptoms. The acid neutralizing capability of available OTC antacids is also quite variable. H₂RAs, on the contrary, have a duration of action of up to 12 h and are useful to prevent and treat occasional episodic heartburn. If combined with an antacid, H₂RAs can quickly treat existing heartburn as well. However, studies have shown that repeated dosing with H₂RAs, as may be necessary for the treatment of frequent heartburn, can lead to tolerance as early as the second day of dosing (8, 9), resulting in diminished efficacy in acid suppression. A study of gastric pH in 28 healthy volunteers showed that mean gastric acid inhibition was similar on the first day of dosing for omeprazole 40 mg and ranitidine 300 mg (8). On the second day of dosing, the degree of gastric acid inhibition with omeprazole increased significantly, while the gastric acid inhibition with ranitidine was significantly attenuated compared with day 1. On day 7 and day 14 of dosing, the omeprazole treatment group exhibited a sustained maximal suppression of gastric acid. In contrast, continued daily treatment with ranitidine resulted in a sustained inhibition on days 7 and 14 that was less than half the degree of gastric acid inhibition noted on day 1. Thus, it is not surprising that consumers with frequent heartburn are dissatisfied with OTC products such as H₂RAs, especially when they are used continuously.

Omeprazole (Ome) has been marketed worldwide since 1988 under various trade names in Europe and, in 1989, was the first proton pump inhibitor (PPI) approved for prescription use in the United States. The dosage formulation, recently approved for OTC status and evaluated in the two clinical trials in this report, is a tablet consisting of multiple enteric-coated pellets formulated with Ome-Mg. The Ome-Mg tablet is approved for R_x

indications in more than 60 countries worldwide, has a similar bioavailability to the oral R_x capsule forms of Ome, and delivers the identical 20 mg of omeprazole as the active ingredient for suppression of acid secretion. Ome-Mg in doses up to 20 mg for the relief of heartburn was also approved for OTC status in Sweden in 1999 and in the UK in 2003. Omeprazole has an extensive history of safe use, including patients in the R_x setting exposed to high doses for prolonged periods of time (10–13). It controls frequent heartburn symptoms and gastric acidity with daily dosing (14), and has a long-lasting effect (more than 24 h) in reducing gastric acid secretion despite its relatively short plasma half-life of 1 h (15). While omeprazole is clearly effective after the first dose, its maximum inhibitory effect on gastric acid is seen after three or more days of dosing (15).

A recent 3-month actual use study demonstrated that consumers used the 14-day omeprazole regimen appropriately in a 'real world' OTC setting (16). Consumers recruited at five shopping mall kiosks were given unlimited opportunity to purchase (and repurchase) a 14-day supply of omeprazole based solely on their understanding of the carton label. Of the 866 subjects who made an initial purchase, over 90% accurately self-selected for frequent heartburn (defined as heartburn symptoms two or more days per week). Subjects also showed 90–100% accuracy on the other selection criteria including 18 years of age or older, not pregnant or nursing, no allergy to omeprazole, and no contraindicated symptoms. In this actual use study, analysis of diary data demonstrated a high degree of compliance to label use instructions with only 3% of subjects taking more than 14 doses without consulting a physician. In addition, 75% of subjects had contact with a physician about their heartburn symptoms before, during or after the study (26% during the study). Overall, these actual use data support that consumers accurately self-select, comply with a 14-day regimen, and appropriately seek physician involvement for longer-term management of frequent heartburn.

The excellent safety record, pharmacodynamic profile and lack of potential for tolerance combine to make 20 mg Ome Mg uniquely well suited for the OTC treatment of frequent heartburn. The novel 14-day regimen-based therapy provides excellent efficacy: nearly 50% experience complete

heartburn relief on day 1, with the degree of efficacy increasing over the first few days of the regimen and then maintained over the entire 14 days. Coupled with actual use data demonstrating appropriate self-selection and compliance with label instructions, these data form the basis for the FDA-approved labelling for Prilosec OTC™, an excellent medication for the OTC marketplace to address unmet consumer needs for the treatment of frequent heartburn.

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