NDA: 21-229 **Date: 9/8/2000**

APPLICANT: AstraZeneca LP

NAME OF DRUG: Prilosec 1 (omeprazole magnesium) 20 mg Tablets.

INDICATION: Treatment and prevention (4-hour versus 2-week) of heartburn.

What are the important statistical issues?

- Neither Study 1997092 nor Study 1997095 shows the superiority of Ome-Mg 20 mg to placebo in the treatment of heartburn.
- Only one study (171) shows the superiority of Omeprazole 20 mg to placebo in the prevention of nocturnal heartburn on the 2-week prevention of heartburn.

I. Indication for the 4-hour prevention of heartburn - Studies 1998005 & 1998006

Comments on the analysis results for Study 1998005

- The efficacy of Ome-Mg 20 mg is borderline significantly better than that of placebo (p=0.057) on 4-hour heartburn-free evaluation (the primary efficacy endpoint) by the sponsor's analysis, reported by Table 8.2.2 in Volume 29.
- However, the 95% two-sided confidence interval for the 5.3% therapeutic gain of Ome-Mg 20 mg versus placebo on 4-hour heartburn-free evaluation is (–0.3%, 10.9%), with lower bound, –0.3%, slightly less than 0.

Comments on the analysis results for Study 1998006

- The efficacy of Ome-Mg 20 mg is significantly better than that of placebo (p=0.004) on 4-hour heartburn-free evaluation (the primary efficacy endpoint) by the sponsor's analysis, reported by Table 8.2.2 in Volume 38.
- Since the primary objective of this Study is achieved, the efficacy of Ome-Mg 10 mg versus placebo is then pursued. The result indicates that the efficacy of Ome-Mg 10 mg is also significantly better than that of placebo (p=0.005) on 4-hour heartburn-free evaluation.

Overall Comments for Studies 1998005 and 1998006

- The superiority of Ome-Mg 20 mg to placebo on 4-hour heartburn-free evaluation (the primary efficacy endpoint) is supported by Study 1998006 (p=0.004).
- The efficacy of Ome-Mg 20 is borderline significantly better than that of placebo (p=0.057) on 4-hour heartburn-free evaluation (the primary efficacy endpoint), reported by Study 1998005. However, the 95% two-sided confidence interval for the 5.3% therapeutic gain of Ome-Mg 20 mg versus placebo on 4-hour heartburn-free

evaluation is (–0.3%, 10.9%), with lower bound, -0.3%, slightly less than 0.

II. Indication for the treatment of heartburn - Studies 1997092 & 1997095

The analysis results and comments for Study 1997092

i.) Sponsor's Analysis Results

Table 2.1.1.1 Primary efficacy analysis on SCR for the first treated episode of heartburn using intent-to-treat patients

TREATMENT GROUP	HTBN-FR RT#	P-VALUE VS. PLACEBO [1]	P-VALUE FOR HOMOG [2]
Placebo (N=627)	29.5% (185/627)		
Ome-Mg 10 (621)	31.5% (195/620)	0.503	0.541
Ome-Mg 20 (N=621)	30.2% (187/620)	0.822	0.386

[1]: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as stratification factor; #: Heartburn-Free rate;
[2]: Breslow-Day test for odds homogeneity across investigators between a treatment vs. placebo.

Table 2.1.1.2 GEE method on SCR with treatment, investigator, and episode as model parameters to compare treatment effects of Ome-Mg 20 vs. Placebo

EPISODE GROUP	ODDS RATIO	95% C.I.	P-VALUE
EPISD1#	1.15	(0.93, 1.4)	0.21
EPISD2&	1.04	(0.82, 1.3)	0.78

#: EPISD1 consists of episodes separated at least 3 days from the most recent episode.
&: EPISD2 consists of episodes separated at least 5 days from the most recent episode.

ii.) Reviewer's Analysis Results

Table 2.1.2.1 Results of GEE method on SCR to compare the efficacy between Ome-Mg 20 and placebo using all treated episodes

PARAMETER	ESTIMATE	P-VALUE
Treatment	0.050	0.66
Pooled Investigator	----#	----
Day	-0.004	0.58
Treatment*Day	0.024	0.009*

#: Not important for this analysis; *: Significant at .05 level.

iii.) Comments on the analysis results for Study 1997092

- The efficacy of Ome-Mg 20 mg is not significantly better than that of placebo (p=0.82) on SCR for the first treated episode (the primary endpoint) reported in Table 2.1.1.1.
- Table 2.1.2.1 shows that the parameter estimate (0.024) of treatment*day is significantly different from zero (p=0.009), indicating the log odds of SCR for OME-Mg 20 mg is a positive trend in favor of the later treatment period. The carryover effect of Ome-Mg 20 mg is thus identified.
- . Table 2.1.1.2 shows that after eliminating the carryover effect, a single dose effect of

Ome-Mg 20 mg tested by groups EPISD1 (p=0.21) and EPISD2 (p=0.78) is not superior to that of placebo.

- From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 mg is not significantly better than that of placebo in the treatment of heartburn through a single dose.
- Since the primary objective of this study uses up .05 significance level and is not supported by the sponsor's primary efficacy analysis on the sustained complete relief evaluation, no significance level (α) left to assess the secondary objective or any other secondary endpoints.

The analysis results and comments for Study 1997095

i.) Sponsor's Analysis Results

Table 2.2.1.1 Primary efficacy analysis on SCR for the first treated episode of heartburn using intent-to-treat patients

TREATMENT GROUP	HTBN-FR RT#	P-VALUE VS. PLACEBO [1]	P-VALUE FOR HOMOG [2]
Placebo (N=602)	29.4% (177/602)*		
Ome-Mg 10 (623)	29.9% (186/623)*	0.810	0.111
Ome-Mg 20 (N=627)	29.2 (183/627)*	0.934	0.001*

[1]: Cochran-Mantel-Haenszel test for a treatment vs. placebo using investigator as stratification factor; #: Heartburn-Free rate;
[2]: Breslow-Day test for odds homogeneity across investigators between a treatment vs. placebo.

Table 2.2.1.2 GEE method on SCR with treatment, investigator, and episode as model parameter to compare treatment effects of Ome-Mg 20 vs. Placebo

EPISODE GROUP	ODDS RATIO	95% C.I.	P-VALUE
EPISD1#	1.07	(0.86, 1.33)	0.535
EPISD2&	0.98	(0.77, 1.25)	0.85

#: EPISD1 consists of episodes separated at least 3 days from the most recent episode.
&: EPISD2 consists of episodes separated at least 5 days from the most recent episode.

ii.) Reviewer's Analysis Results

Table 2.2.2.1 Results of GEE method on SCR to compare the efficacy between Ome-Mg 20 and placebo using all treated episodes

PARAMETER	ESTIMATE	P-VALUE
Treatment	0.13	0.27
Pooled Investigator	----#	----
Day	-0.004	0.55
Treatment*Day	0.026	0.014*

#: Not important for this analysis; *: Significant at .05 level.

iii.) Comments on the analysis results for Study 1997095

- The efficacy of Ome-Mg 20 mg is not significantly better than that of placebo (p=0.934) on SCR for the first treated episode (the primary endpoint) reported in

Table 2.2.1.1.

- Table 2.2.2.1 shows that the parameter estimate (0.026) of treatment*day is significantly different from zero (p=0.014), indicating the log odds of SCR for OME-Mg 20 mg is a positive trend in favor of the later treatment period. The carryover effect of Ome-Mg 20 mg is thus identified.
- Table 2.2.1.2 shows that after eliminating the carryover effect, a single dose effect of Ome-Mg 20 mg tested by groups EPISD1 (p=0.535) and EPISD2 (p=0.85) is not superior to that of placebo.
- From the results of the sponsor's and this reviewer's analyses, it can be concluded that the effect of Ome-Mg 20 mg is not significantly better than that of placebo in the treatment of heartburn through a single dose.
- Since the primary objective of this study uses up .05 significance level and is not supported by the sponsor's primary efficacy analysis on the sustained complete relief evaluation, no significance level (α) left to assess the secondary objective or any other secondary endpoints.

Overall Comments for Studies 1997092 and 1997095

- From the results of the sponsor's and this reviewer's analyses, it can be concluded that the treatment of heartburn is not supported.

III. Indication for the two-week prevention of heartburn - Studies 171 and 183

Overall Comments for Studies 171 and 183

- The effects of Ome-Mg 20 mg and Ome-Mg 10 mg are both significantly better than that of placebo in the two-week prevention of heartburn. However, only one study 171 shows the superiority of omeprazole to placebo in the two-week prevention of nocturnal heartburn.

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Concur: Dr. Permutt Thomas Permutt 9/8/00

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