observation was carried forward to be the week 4 and week 8 value. If the patient's last data was for week 4 or week 6, that observation was carried forward to be the week 8 value. If the patient had week 8 data but not week 4 data, that patient was left out of the week 4 analysis.

[NOTE: Once again, the ITT [-] analysis was the most conservative because patients who only had baseline data were identified similarly to the ITT [+] patients except that their missing data was expressed as patients not being healed. As in study -300-US, the MO's main conclusions on efficacy are based on analysis of the ITT [-] population. Results of analyses of the ITT [+] population are also included in the present review for completeness. However, neither results of analyses of the MITT nor the VFE populations are considered in the current review.]

f) Healing of Erosive Esophagitis (Table 26)

i) Healing of EE in ITT [-] and [+] populations analysis

Because the results of evaluations in all four population analyses were similar and allowed practically the same conclusions to be arrived at, only results for the ITT [-] population and those for the ITT [+] population are displayed in Table 26. The comments that follow apply to results for the ITT [-] population (upper panel of Table 26). In addition to the EE healing rates per treatment group, the therapeutic gains resulting from comparisons between each PANTO group and NIZ and between one PANTO group against the other, are shown on the right hand side of this Table.

After 4 weeks of treatment, both doses of PANTO (20 and 40 mg QD) were significantly more effective than NIZ in the healing of EE lesions. The therapeutic gains were 40% and 44% for the 20 and 40 mg PANTO. respectively. In this study, the therapeutic gain of 40 vs 20 mg PANTO was a modest 5% and statistically insignificant.

Similar conclusions can be drawn when considering EE healing after 8 weeks of treatment. Each of the dose levels of —— were more effective than NIZ in the healing of EE lesions, with therapeutic gains of 37% and 38%, respectively. However, the effects of the 40 mg PANTO dose could not be differentiated from those of the 20 mg dose (therapeutic gain = 0.3%; p-value=N.S.).

Similar conclusions were reached when evaluating results of analyses of the ITT [+] population (see lower panel of Table 26).

TABLE 26

Study GMR-32023 (3001A1-301-US)

Erosive Esophagitis Healing Rates as a Function of Treatment Group and Length of Treatment

I. ITT [-] POPULATION ANALYSIS						
	NIZ (mg BID)	PANTO (mg QD)		Therapeutic Gain (%)/[Statistical Significance (p-value)]		
WEEK	150	20	40	20 mg vs NIZ	40 mg vs NIZ	40 mg vs 20 mg
4	[n=78]	[n=75]	[n=77]			
	16 (20.5%)	45 (60.0%)	50 (64.9%)	39.5% [<0.001]	44.4% [<0.001]	4.9% [N.S.]
8	[n=82]	[n=80]	[n=81]			
	30 (36.6%)	59 (73.8%)	60 (74.1%)	37.2% [<0.001]	37.5% [<0.001]	0.3% [N.S.]
II. ITT [+] POPULATION ANALYSIS						
4	[n=78]	[n=75]	[n=77]			
	24 (30.8%)	50 (66.7%)	53 (68.8%)	35.9% [<0.001]	38.0% [<0.001]	2.1% [N.S.]
8	[n=82]	[n=80]	[n=81]			
	38 (46.3%)	64 (80.0%)	63 (77.8%)	33.7% [<0.001]	31.5% [<0.001]	-2.2% [N.S.]

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ii) Healing rates controlling for baseline severity of EE and *H. pylori* status

When controlling for baseline severity of EE and separately controlling for baseline *H. pylori* status, the results were similar to those mentioned above for the unstratified analyses: the CMH analyses stratified by *H. pylori* status yielded the same conclusions as the non-stratified analysis presented above. Patients taking each of the two doses of PANTO had significantly greater healing rates than those taking NIZ at all time points in all populations. The two PANTO groups could not be differentiated from each other. The healing rates of patients treated with either dose of PANTO were significantly greater than those of patients treated with NIZ when the *H. pylori* status was [-] and these results occurred no matter which patient population was analyzed. For patients in all populations who had positive *H. pylori* status, the healing rates were not significantly different between the 20 mg PANTO dose group and the NIZ dose group at 4 weeks. The sample sizes used for the analysis (16 versus 13 for the ITT [-] population) were small and the healing rates of 56% and 23% were not found to be significantly different. The healing rates of *H. pylori* positive patients receiving 40 mg of PANTO were significantly greater at 4 weeks than the healing rates of patients receiving NIZ for any patient population.

iii) Healing rates in relation to initial severity of EE (Table 27)

As noted in Table 24, the population of patients who at randomization had EE of grade 2 (mild) was 65%, those with EE grade 3 (moderate) or 4 (severe) accounted for 26% and 9% of the patients, respectively, and the three experimental groups were comparable to each other with regards to the distribution of patients in these substrata. The treatment groups were compared with regards to response within each severity category. As shown in Table 27, in the ITT [-] population analyses, despite the smaller sample sizes in the subgroups, therapeutic gains and statistically significant differences seen for each of the two severity groups (2 and ≥3), were similar to those observed in the combined population.

In patients with grade 2 (mild) EE at entry, after 4 weeks of treatment, each of the dose levels of PANTO (20 and 40 mg QD) were significantly more effective than NIZ in the healing of EE lesions, with therapeutic gains of 48.2% and 56.2%, respectively. The two PANTO doses could not be differentiated from each other.

Similar conclusions can be drawn when considering healing rates at 8 weeks in those patients who had grade 2 EE at randomization. Each of the two PANTO doses was significantly higher than the 49% NIZ response, with corresponding therapeutic gains of 37% and 39%, but no difference between the 20 and the 40 mg PANTO was observed.

Healing rates in those patients with initial severity of grade≥3 (**moderate/severe** EE are displayed in the lower panel of Table 27. At 4 weeks, both PANTO treatment groups were statistically higher than NIZ in the healing of EE lesions with therapeutic gains of 29% and 32%, respectively. At this time, the 40 mg dose could not be differentiated from the 20 mg PANTO dose.

TABLE 27

Study GMR-32023 (3001A1-301-US)

Erosive Esophagitis Healing Rates as a Function of Treatment Group, Length of Treatment and Initial Severity of EE

Week	NIZ (mg BID)	PANTO (mg QD)		Therapeutic Gain (%)/[Statistical Significance (p-value)]		
	150	20	40	20 mg vs NIZ	40 mg vs NIZ	40 mg vs 20 mg
I. PATIENTS WITH INITIAL SEVERITY OF GRADE 2 EE						
4	[n=56]	[n=48]	[n=47]			
	15 (26.8%)	36 (75.0%)	39 (83.0%)	48.2% [<0.001]	56.2% [<0.001]	8.0% [N.S.]
8	[n=57]	[n=51]	[n=50]			
	28 (49.1%)	44 (86.3%)	44 (88.0%)	37.2% [<0.001]	38.9% [<0.001]	1.7% [N.S.]
II. PATIENTS WITH INITIAL SEVERITY OF GRADE ≥3 EE						
4	[n=22]	[n=27]	[n=30]			
	1 (4.5%)	9 (33.3%)	11 (36.7%)	28.8% [0.015]	32.2% [0.008]	3.4% [N.S.]
8	[n=25]	[n=29]	[n=31]			
	2 (8.0%)	15 (51.7%)	16 (51.6%)	43.7% [<0.001]	43.6% [<0.001]	-0.1% [N.S.]

Reviewer's Table

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At 8 weeks, therapeutic gains of 44% for each PANTO dose over NIZ were seen in this subgroup (EE grade ≥3 at randomization) but virtually no differences were observed between the 40 and the 20 mg PANTO dose.

iv) Healing rates by investigational site (Table 28)

Listed in the upper panel of Table 28 are the healing rates at 4 and 8 weeks for the 40 mg PANTO group and NIZ at the 11 sites that enrolled the majority of patients (see IX. 10. a) above]. No specific center appeared to drive the results. In statistical analyses, the results of which are displayed in the lower panel of Table 28, sites with small patient totals were dropped from this analysis if there were no patients in one of the Tx groups being compared or all patients in each group had the same response (i.e. all healed or all not healed). The results were consistent with those based on the pooled analysis not stratified by study site. As seen in the lower panel of Table 28, significant differences between each of the PANTO treatment groups and NIZ were found at Week 4 and Week 8. There was no statistically significant difference between the 40 and 20 mg doses of PANTO.

TABLE 28
Study GMR-32023 (3001A1-301-US)

EE Healing Rates by Investigational Site

I. Response With NIZ and 40 mg PANTO at 4 and 8 Weeks in Those Centers That Enrolled ≥10 Patients Each

Site 301-	Week 4		Week 8	
	NIZ 150 mg BID	PANTO 40 mg QD	NIZ 150 mg BID	PANTO 40 mg QD
99	1/11 (9%)	7/12 (58%)	3/12 (25%)	10/12 (83%)
96	1/9 (11%)	4/8 (50%)	3/10 (30%)	6/10 (60%)
81	0/6 (0%)	4/6 (67%)	0/6 (0%)	4/7 (57%)
85	1/5 (20%)	4/5 (80%)	2/5 (40%)	4/5 (80%)
80	0/4 (0%)	2/4 (50%)	1/4 (25%)	4/4 (100%)
87	1/4 (25%)	3/4 (75%)	1/4 (25%)	3/4 (75%)
A8	1/3 (33%)	3/4 (75%)	2/4 (50%)	3/4 (75%)
95	1/4 (25%)	2/4 (50%)	1/4 (25%)	3/4 (75%)
AO	0/3 (0%)	2/4 (50%)	1/3 (33%)	3/4 (75%)
83	0/3 (0%)	4/4 (100%)	0/3 (0%)	4/4 (100%)
86	1/4 (25%)	2/3 (67%)	2/4 (50%)	2/3 (67%)

II. p-values for Pairwise Comparisons (CMH tests) Based on the Number of Specified Sites [in ( )]

40 mg PANTO vs NIZ	<0.001 (19)	<0.001 (16)
20 mg PANTO vs NIZ	<0.001 (18)	<0.001 (18)
40 mg vs 20 mg PANTO	N.S. (17)	N.S. (16)

NOTE: The sponsor's statistical analyses by site also provided a test of the homogeneity of results across study sites. This test yielded a statistically significant result for the comparison of the two doses of pantoprazole at week 4, indicating lack of consistency across sites. At that time, the number of sites at which the healing rate was higher for 40 mg than for 20 mg was equal to the number of sites at which the reverse was true. A more detailed discussion of results by investigation... was provided in the sponsor's Statistical Appendix.

g) Results of Secondary Efficacy Assessments

i) Overall absence of GERD symptoms

The sponsor made use of survival analysis technique to produce curves (not shown in this review) for each Tx group representing the time to **persistent absence** of symptoms. The **median** time to persistent absence of symptoms (i.e. the number of days at which 50% of the patients in the group had obtained a persistent lack of symptoms), as estimated by the survival analysis was:

Treatment Group	Median Time
NIZ 150 mg BID	N/E
PANTO 20 mg	31
PANTO 40 mg	39

N/E = No estimate could be obtained for the NIZ group because less than 50% of the patients achieved persistent absence of symptoms.

- The percentages displayed in Table 29 represent the proportion of patients with persistent absence of any symptom. Significantly more patients treated with PANTO 20 mg QD obtained persistent absence of symptoms than NIZ from the first study day through Day 63. Greater percentages of patients treated with 40 mg of PANTO than with NIZ had persistent absence of symptoms from Day 2 through Day 63. There were no significant differences between the two PANTO doses in percentages of patients with persistent absence of symptoms at any time.

TABLE 29
Study GMR-32023 (3001A1-301-US)

Cumulative Proportion (%) of Patients[a] With Persistent Absence of Any Symptom

	NIZ (mg QD)	PANTO (mg QD)	
Day	150 [n=80]	20 [n=78]	40 [n=79]
1	0	8% >NIZ	5%
2	0	9% >NIZ	6% >NIZ
3	0	13% >NIZ	9% >NIZ
4	0	13% >NIZ	9% >NIZ
5	0	14% >NIZ	10% >NIZ
6	0	15% >NIZ	11% >NIZ
7	1%	15% >NIZ	11% >NIZ
14	4%	23% >NIZ	22% >NIZ
21	8%	32% >NIZ	28% >NIZ
28	13%	49% >NIZ	42% >NIZ
35	14%	53% >NIZ	46% >NIZ
42	14%	54% >NIZ	49% >NIZ
49	19%	54% >NIZ	53% >NIZ
56	29%	65% >NIZ	61% >NIZ
63	35%	68% >NIZ	65% >NIZ

a) Proportion of patients providing symptom data per Tx group. Statistically significant differences between PANTO group and NIZ indicated by the sign > (meaning: superior to NIZ).

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ii) Absence of daytime heartburn (Table 30)

- Each of the PANTO dose groups had greater percentages of patients with persistent absence of daytime HB than NIZ, from the second study day throughout Day 63. There were no significant differences between the two PANTO doses in percentages of patients with persistent absence of daytime HB at any time.

TABLE 30
Study GMR-32023 (3001A1-301-US)

Cumulative Proportion (%) of Patients[a] With Persistent Absence of Daytime Heartburn

	NIZ (mg BID)	PANTO (mg QD)	
Day	150 [n=80]	20 [n=78]	40 [n=79]
1	8%	15%	15%
2	8%	22% >NIZ	22% >NIZ
3	8%	26% >NIZ	23% >NIZ
4	8%	27% >NIZ	23% >NIZ
5	8%	29% >NIZ	23% >NIZ
6	8%	29% >NIZ	24% >NIZ
7	8%	29% >NIZ	24% >NIZ
14	9%	35% >NIZ	34% >NIZ
21	14%	47% >NIZ	44% >NIZ
28	21%	62% >NIZ	56% >NIZ
35	26%	67% >NIZ	59% >NIZ
42	26%	71% >NIZ	65% >NIZ
49	34%	71% >NIZ	66% >NIZ
56	46%	78% >NIZ	70% >NIZ
63	51%	82% >NIZ	72% >NIZ

a) Proportion of patients providing symptom data per Tx group. Statistically significant differences between PANTO groups and NIZ indicated by the sign > (meaning superior to NIZ).

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iii) Absence of nighttime heartburn (Table 31)

- With both PANTO treated doses, significantly greater percentages of patients experienced persistent absence of nighttime HB from the first day of the trial throughout Day 56. There were no significant differences between the two PANTO doses in percentages of patients with persistent absence of nighttime HB at any time.

TABLE 31
Study GMR-32023 (3001A1-301-US)

Cumulative Proportion (%) of Patients[a] With Persistent Absence of Nighttime Heartburn

	NIZ (mg BID)	PANTO (mg QD)	
Day	150 [n=80]	20 [n=78]	40 [n=79]
1	8%	23% >NIZ	20% >NIZ
2	9%	27% >NIZ	22% >NIZ
3	10%	29% >NIZ	25% >NIZ
4	10%	31% >NIZ	29% >NIZ
5	10%	33% >NIZ	30% >NIZ
6	10%	33% >NIZ	32% >NIZ
7	13%	35% >NIZ	32% >NIZ
14	15%	45% >NIZ	43% >NIZ
21	20%	50% >NIZ	48% >NIZ
28	33%	63% >NIZ	62% >NIZ
35	38%	68% >NIZ	66% >NIZ
42	40%	72% >NIZ	70% >NIZ
49	48%	73% >NIZ	75% >NIZ
56	60%	82% >NIZ	78% >NIZ
63	70%	83%	84%

a) Proporation of patients providing symptom data per Tx group. Statisticaliy significant differences between PANTO groups and NIZ indicated by the sign > (meaning: superior to NIZ)

iv) Absence of regurgitation (Table 32)

- With both PANTO-treated doses, significantly greater percentages of patients experienced persistent absence of regurgitation from the first day of the trial throughout Day 49. As per other symptoms, there were no significant differences between the two PANTO doses in percentages of patients with persistence absence of regurgitation at any time.

TABLE 32
Study GMR-32023 (3001A1-301-US)

Cumulative Proportion (%) of Patients[a] With Persistent Absence of Regurgitation

	NIZ (mg BID)	PANTO (mg QD)	
Day	150 [n=80]	20 [n=78]	40 [n=79]
1	13%	32% >NIZ	33% >NIZ
2	15%	37% >NIZ	34% >NIZ
3	15%	37% >NIZ	39% >NIZ
4	15%	40% >NIZ	39% >NIZ
5	15%	40% >NIZ	42% >NIZ
6	15%	44% >NIZ	42% >NIZ
7	15%	44% >NIZ	44% >NIZ
14	21%	51% >NIZ	52% >NIZ
21	28%	53% >NIZ	58% >NIZ
28	35%	69% >NIZ	67% >NIZ
35	40%	73% >NIZ	73% >NIZ
42	46%	74% >NIZ	75% >NIZ
49	63%	78% >NIZ	78% >NIZ
56	71%	81%	84%
63	78%	85%	85%

a) Proportion of patients providing symptom data per Tx group. Statistically significant difference between PANTO groups and NIZ indicated by the sign > (meaning: superior to NIZ).

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v) Absence of dysphagia (Table 33)

- The proportion of patients with persistent absence of dysphagia gradually increased during the course of the trial and was ca. 94% for all Tx groups at Day 63. There was no significant differences between the groups in percentages of patients with persistent absence of dysphagia at any time except on Day 21, a finding without clinical importance.

TABLE 33
Study GMR-32023 (3001A1-301-US)

Cumulative Proportion (%) of Patients[a] With Persistence Absence of Dysphagia

Day	NIZ (mg BID) 150 [n=80]	PANTO (mg QD) 20 [n=78]	PANTO (mg QD) 40 [n=79]
1	50%	65%	56%
2	54%	67%	59%
3	55%	68%	63%
4	56%	68%	65%
5	56%	71%	66%
6	58%	72%	68%
7	58%	73%	68%
14	64%	78%	75%
21	66%	81% >NIZ	81% >NIZ
28	74%	86%	87%
35	80%	87%	90%
42	84%	88%	90%
49	88%	90%	90%
56	93%	91%	92%
63	95%	94%	92%

a) Proportion of patients providing symptom data per Tx group. Statistically significant differences between PANTO groups and NIZ indicated by the sign > (meaning: superior to NIZ).

vi) Antacid use (Table 34)

- Each of the two doses of PANTO was significantly different from NIZ ($p<0.001$): the patients treated with pantoprazole used less Gelusil than the NIZ patients (Table 34). Gelusil usage was similar for the two PANTO groups.

TABLE 34
Study GMR-32023 (3001A1-301-US)

Median Gelusil Tablet Usage

Treatment Group	n	Total Tablets Median (25P-75P)[a]	Tablets per Day Median (25P-75P)
NIZ 150 mg BID	80	67.5 (24.0 – 142.5)	1.61 (0.42 – 3.02)
PANTO 20 mg QD	79	21.0 (3.0 - 65.0)	0.47 (0.07 – 1.88)
PANTO 40 mg QD	78	18.5 (5.0 - 61.0)	0.58 (0.14 – 1.44)

a) 25th through 75th percentiles.

h) Results of Safety Evaluations

i) Extent of exposure (Table 35)

Depicted in this Table is the cumulative duration of exposure of ——— , and NIZ in Study –301-US. For the PANTO doses, the starting number of patients (161=100%) was the same during the first 2 weeks of the trial but starts to decrease steadily from the third week onwards, with a marked decrease after Week 4 (second endoscopy which may have shown healing of EE and may have been a reason to W/D the patient from the trial), so that by Week 8 there remained only 49 patients (30%).

TABLE 35
Study GMR-32023 (3001A1-301-US)

Cumulative[a] Duration of Exposure to Pantoprazole and Nizatidine

Drug Dose	Cumulative Duration of Exposure (Weeks)									
	≥1 day	≥ 1	≥ 2	≥ 3	≥ 4	≥ 5	≥ 6	≥ 7	≥ 8	≥ 9
NIZ (BID) (150 mg)	82 (100)	81 (99)	81 (99)	80 (98)	77 (94)	62 (76)	56 (68)	55 (67)	52 (63)	13 (16)
PANTO (mg QD)										
Any dose	161 (100)[b]	161 (100)	161 (100)	158 (98)	152 (94)	66 (41)	55 (34)	51 (32)	49 (30)	11 (7)
20	80 (100)	80 (100)	80 (100)	78 (98)	76 (95)	33 (41)	31 (39)	28 (35)	26 (33)	5 (6)
40	81 (100)	81 (100)	81 (100)	80 (99)	76 (94)	33 (41)	24 (30)	23 (28)	23 (28)	6 (7)

This Table corresponds to sponsor's Table 10. 1A, with minor modifications.
a Cumulative exposure is the number of patients (%) who took the drug for at least the time interval defined.
b Number in parentheses is the percentage of patients exposed to PANTO or NIZ.

ii) Deaths/other serious and potentially serious AEs

- No patients died during the trial.
- As summarized below, there were 4 who experienced SAEs:

Treatment Body System	Patient Number	Age (y)/ Sex	Days on Therapy	SAE	Remarks
NIZ 150 mg BID					
Body as a Whole	30181-0018	54 M	35	Abdominal pain	Possibly related. Resulted in D/C
Body as a whole Digestive system	30185-0012	23 M	54	Abdominal pain Nausea, vomiting	Probably related. He completed the trial.
PANTO 20 mg QD					
Nervous system	30185-0030	46 F	30	Depression	Unrelated. Pt. completed the trial.
PANTO 40 mg QD					
Skin and Appendages	30186-0001	30 M	60	Severe Rash Mild Rash	Probably related (both events) Skin Bx showed non-specific findings (focal vacuolar interface dermatitis with associated perivascular and perifollicular lymphocytic infiltrate). He was withdrawn from the study.

- From the above, **severe rash** should be included in the labeling.

iii) AEs leading to discontinuation

- AEs caused D/C of Tx for the following 3 pts.:

  - PANTO 40 mg QD
    Pt. 30186-001: rash (see above)

  - NIZ 150 mg BID
    Pt. 30181-0018: abdominal pain (see above)

    Pt. 30187-0005: dyspepsia
    [The primary reason for withdrawal of this patient was **lack of efficacy**. This patient was accordingly tabulated under "unsatisfactory response" in the efficacy evaluations. The patient is mentioned above because the secondary reason for withdrawal was "Adverse Event – Dyspepsia"].

iv) Adverse events

- One or more AEs were reported by the following proportion of patients in the 3 arms of the trial. Also listed are the proportions of patients reporting AEs which the investigator considered possibly, probably or definitely related to test medication.

	Proportion of Pts. Reporting One or More AEs	Drug Relationship Listed as Possible, Probable or Definite
NIZ (150 mg BID)	54 (66%)	18 (22%)
PANTO (20 mg QD)	43 (54%)	12 (15%)
PANTO (40 mg QD)	48 (59%)	19 (23%)

- Overall, TEAEs were distributed as follows:

NIZ (150 mg BID)	48 (59%)
PANTO (20 mg QD)	39 49%
PANTO (40 mg QD)	44 54%

- Most commonly reported TEAEs (reported by at least 3% of pts. in any Tx group), grouped by body system, are shown in Table 36. The most common TEAEs for all Tx groups, were **headache and diarrhea**. No statistically significant difference was seen in the incidence of either headache or diarrhea between patients receiving PANTO vs those receiving NIZ. Furthermore, there was no statistically significant difference in the incidence of diarrhea or headache between the patients receiving PANTO (either 40 or 20 mg) and those receiving NIZ. Also, there was no statistically significant difference in the incidence of diarrhea between the patients who took 20 mg or PANTO and those who took 40 mg.

TABLE 36
Study GMR-32023 (3001A1-301-US)

Commonly Reported (≥3%) TEAE Number (%) of Patients

Body System Adverse Event	NIZ (mg BID) 150 [n=82]	PANTO (mg QD) 20 [n=80]	PANTO (mg QD) 40 [n=81]	p-Value[a]
Any AE (1 or more)	48 (59)	39 (49)	44 (54)	N.S.
Body as a whole	31 (38)	24 (30)	22 (27)	N.S.
Abdominal pain	6 (7)	4 (5)	5 (6)	N.S.
Accidental injury	6 (7)	6 (8)	3 (4)	N.S.
Flu syndrome	1 (1)	3 (4)	0	N.S.
Headache	**19 (23)**	**10 (13)**	**15 (19)**	N.S.
Infection	4 (5)	4 (5)	1 (1)	N.S.
Digestive system	21 (26)	14 (18)	18 (22)	N.S.
Constipation	2 (2)	3 (4)	1 (1)	N.S.
Diarrhea	**9 (11)**	**8 (10)**	**6 (7)**	N.S.
Flatulence	0	3 (4)	4 (5)	N.S.
Gastroenteritis	1 (1)	0	3 (4)	N.S.
Nausea	2 (2)	2 (3)	4 (5)	N.S.
Vomiting	3 (4)	3 (4)	3 (4)	N.S.
Nervous system	7 (9)	4 (5)	7 (9)	N.S.
Dizziness	5 (6)	0	2 (2)	N.S.
Respiratory system	12 (15)	7 (9)	8 (10)	N.S.
Pharyngitis	5 (6)	3 (4)	2 (2)	N.S.
Rhinitis	3 (4)	1 (1)	2 (2)	N.S.
Subysutus	2 (2)	2 (3)	3 (4)	N.S.

a) Fisher's exact test

v) Changes in laboratory parameters

- The numbers of treated patients with potentially clinically important test results were summarized in sponsor's Table 10.4.1.1A. The data were grouped by laboratory assessment and patient identification number. These data revealed no clinically important differences between treatment groups.

- In general, the changes in laboratory parameters reflected sporadic or transient increases or decreases that returned to baseline values during the course of therapy.

vi) Changes in vital signs/routine P.E. and weights

- There were no clinically important or statistically significant changes in vital signs. Although there were several statistically significant changes for weight in the PANTO groups, there were no significant differences in mean values among the Tx groups. There were no clinically significant changes in routine P.E. from individual patients P.E. measurement.

vii) Changes in serum gastrin[10] levels

- Baseline serum gastrin levels were similar across Tx groups for both positive and negative *H. pylori* status. The highest serum gastrin levels were recorded for patients positive for *H. pylori* at baseline and treated with 40 mg of PANTO (see below). Patients negative for *H. pylori* at baseline had lower serum gastrin levels in PANTO treatment groups compared to those patients positive for *H. pylori* at baseline. Serum gastrin levels reflected a dose response effect regardless of *H. pylori* status at baseline.

- The 40 mg PANTO group had greater serum gastrin values than 20 mg group at 4 weeks.

- Both the 40 mg and 20 mg groups had greater values than the NIZ group. A listing of patients with serum gastrin levels greater than 150 pg/ml was provided in sponsor's NIZ Supportive Table 17.

Median Serum Gastrin Levels (pg/ml)

	H. pylori Status [+]			*H. pylori* Status [-]		
Tx Group	Median [n] Baseline	Median [n] 4-week	Median [n] 8-week	Median [n] Baseline	Median [n] 4-week	Median [n] 8-week
NIZ 150 mg BID	53 [13]	49.5 [6]	48 [8]	48 [65]	52.5 [30]	53 [43]
PANTO 20 mg QD	46 [15]	75 [11]	63.5 [6]	48 [63]	56 [42]	51 [22]
PANTO 40 mg QD	65 [13]	146 [9]	64 [1]	47 [65]	70 [49]	57 [21]

viii) EKG changes

No patient was found to have EKG changes of clinical importance.

ix) Gastric inflammation changes

Changes in inflammation were stratified by *H. pylori* status and biopsy zone (midbody, prepyloric). The sponsor summarizes this information in their Tables 10.6.2A and 10.6.2B. It is noted that even though less than 20% of the patients were *H. pylori* positive, most of the changes of 2 or more in the gastric inflammation score occurred in these patients. In the midbody zone, most of the changes of 2 or more were increases, and in the prepyloric zone most of the changes were decreases. In both zones, changes of 2 or more were more frequent in patients taking PANTO than in patients taking NIZ.

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[10] The data for the serum gastrin levels are to serve as a baseline for the maintenance study.

11. Sponsor's Conclusions

"The results of this study indicate that pantoprazole in doses of 20 or 40 mg was significantly more effective than nizatidine in treating erosive esophagitis. At both 4 and 8 weeks of therapy, the healing rates for patients treated with pantoprazole were always greater than those for patients treated with nizatidine, regardless of baseline *H. pylori* status (positive or negative) or disease severity. All treatments were well tolerated. One (1) patient (Patient 30186-0001) receiving pantoprazole 40 mg QD reported an adverse event which caused withdrawal from the study. This patient, a 30-year old man, had a drug eruption associated with photosensitivity. No significant drug-related differences between the treatments were seen in the safety analysis."

12. Reviewer's Additional Comments

Clinical trial under Protocol –301-US is the second critical multicenter study submitted by the sponsor of this NDA in support of the approval of orally administered pantoprazole for the "short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD)". This U.S. trial consisted of three parallel arms: two fixed doses of PANTO (20 or 40 mg once-a-day) and nizatidine (——— , 150 mg twice-a-day), and H_2-receptor antagonist.

The study was well-designed. NIZ is an adequate positive control because this drug ——— the same indication the sponsor is pursuing and it is being tested at the recommended oral doses of 150 mg twice-a-day. It is worth noting, as summarized in Table 1 (Section 1.A of this review), that there are no available data on the healing rates of NIZ at 4 or 8 weeks per se. However, in one study, healing rates with NIZ at 3 and 6 weeks were 16% and 32%, respectively; these represented therapeutic gains of 9% and 16%, respectively, over PL (3-week response = 7%; 6-week response=16%). In another study, healing rates with NIZ at 6 and 12 weeks, were 21% and 29%, respectively; these represented therapeutic gains of 10% and 16%, respectively, over PL (6-week response=11%; 12-week response=13%). From this information, it can be inferred that the healing rates with NIZ 150 mg BID at 4 weeks would be between 16% and 32%; those at 8 weeks would be between 21% and 29%.

The hypothesis tested in study –301-US was that 4 to 8 weeks of PANTO 40 mg once daily is more effective than the approved NIZ (150 mg BID) in the healing of EE and the rapid relief of associated daytime and nighttime heartburn and other symptoms associated with GERD. The pre-study estimates of healing rates were 80% for PANTO 20 mg, 90% for PANTO 40 mg and 35% for NIZ. Based on the considerations mentioned above, the estimated healing rates with NIZ (35%) is not unreasonable. Similarly, based on results of study –300-US, the expected therapeutic gains of PANTO over NIZ (45% for PANTO 20 mg and 55% for PANTO 40 mg, respectively) do not seem unrealistic.

Study –301-US made use of a Protocol that was, in most respects, similar to the Protocol used in study –300-US. Twenty-six domestic centers participated and a total of 243 patients were randomized into the three groups of patients: either PANTO 20 mg once-a-

day, PANTO 40 mg once-a-day or RAN 150 mg twice-a-day, with a treatment allocation of 1:1:1. Primary objectives of the trial were to compare healing rates of the two drugs at 4 and 8 weeks.

The study was apparently well executed. The inclusion-exclusion criteria were adequate to minimize the effects of potential confounders. The trial was rendered double-blind by using a double-dummy technique. Block randomization was done and each block consisted of 6 numbers, 2 for each treatment group. Each study site was provided with a block (or blocks) of random numbers and these were assigned consecutively, except in 2 out of 244 patients. This randomization process accomplished three well-balanced groups showing comparability in all aspects that may influence efficacy results: number of patients per group (NIZ, n=82; PANTO 20 mg QD, n=80; and PANTO 40 mg QD, n=81), age, gender distribution, ethnic origin, weight, height, severity of erosive esophagitis and *H. pylori* status at randomization, *H. pylori* infection (82% of the patients were *H. pylori* [-] while 18% were *H. pylori* [+]), and common concomitant medications. The primary diagnosis of these patients was erosive esophagitis and this was mostly (65%) of the grade 2 (mild type); grade 3 (moderate)=25.9%; grade 4 (severe)=only 9.1%). The condition was manifested chiefly by mild to moderate GERD symptoms. Analyses of results included evaluations in ITT, MITT and VFE populations. As in study –300-US, the reviewer's comments emphasize results of analyses in the ITT [-] population because this was the most conservative statistical approach: patients who had missing endoscopic data were expressed as patients not being healed. [However, results of analyses in the ITT [+], MITT and VFE populations, allowed the same conclusions on efficacy as those arrived at using the ITT population.] Again, as in study –300-US, although the sponsor's relative day ranges for endoscopy were wider than desirable, it does not seem that narrower time intervals for endoscopy would have a significant impact on results.

Analysis in the ITT [-] population showed that both doses of PANTO (20 and 40 mg QD) were significantly more effective than NIZ in the healing of lesions of erosive esophagitis [as mentioned above, these results were confirmed in all populations analyzed]. In the ITT [-], at 4 weeks of treatment, the healing rates in the PANTO groups (60% and 64.9%, respectively) were both significantly higher than the NIZ group (20.5%). The resulting therapeutic gains [PANTO > NIZ] were 39.5% and 44.4%, respectively, both highly statistically significant **(p<0.001)**. At 4 weeks, the 40 mg PANTO dose was not statistically different from the 20 mg dose. The clear superiority of each PANTO dose over NIZ was maintained at 8 weeks of treatment: the therapeutic gains for each dose over NIZ (37.2% and 37.5%, respectively) were not very different from those seen at 4 weeks but still, the response rates with PANTO in comparison to NIZ were both highly statistically significant **(p<0.001)**. Again, at 8 weeks, PANTO 40 mg QD was not better than 20 mg QD. So, results of EE healing rates at both, 4 and 8 weeks of treatment demonstrated, very convincingly, superiority of —— (both doses) to NIZ, with a very robust statistical strength **(p<0.001)**.

In this trial, the results of erosive esophagitis healing rates taking into consideration the initial severity of the esophageal lesions, allow the same conclusions drawn by the

reviewer on results in study –300-US: even with PANTO, **more severe lesions are more difficult and take longer time to heal.** The response to NIZ in patients whose initial esophagitis was grade 2 (mild) was much higher (26.8% at 4 weeks and 49.1% at 8 weeks) than in those whose initial esophagitis was grade ≥3 (moderate to severe) (4.5% at 4 weeks and only 8% at 8 weeks). Indeed, among patients with initial moderate to severe esophagitis, NIZ 150 mg BID is behaving **like a placebo** (see results for PL in this stratum, study –300-USA). But the superiority of both PANTO doses over NIZ is clearly demonstrated regardless of disease severity at baseline. This in spite of the fact that one dose of PANTO could not be differentiated from the other. For instance, with 40 mg QD, in patients whose esophagitis was grade 2 (mild) at baseline, the therapeutic gain of 56.2% decreased to 38.9% at 8 weeks. Conversely, in those whose esophagitis at baseline was grade ≥3 (moderate to severe) the therapeutic gain (over NIZ) was 32.2% at 4 weeks and this increased to 43.6% with a further 4 weeks of treatment. However, as in study –300-US, since there were not too many patients with grade 4 at baseline included in the ≥3 pooled category, the reviewer concludes that PANTO 40 mg provided the greatest healing rates for both mild and moderate esophagitis. Experience with esophagitis of the severe (Grade 4) type is too limited and no firm conclusions can be drawn at this point in time.

With respect to EE symptoms, the three treatment groups were comparable at baseline. Both doses of PANTO were significantly more efficacious than NIZ in assessment of the effects on symptoms, a secondary parameter of efficacy. In this regard, the effects of the 20 mg PANTO dose could not be differentiated from those of the 40 mg dose. Starting on the first week of therapy, the PANTO 40 mg dose was significantly more efficacious than NIZ in the persistent absence of any symptoms (an effect that lasted up to Day 63), daytime heartburn (also up to Day 63), nighttime heartburn (up to Day 56) and regurgitation (up to Day 49). Both PANTO-treated groups used significantly ($p<0.001$) fewer Gelusil tablets than those in the NIZ group, but the two PANTO groups could not be differentiated from each other in this antacid usage.

In study 301-US, results of safety evaluations confirmed those in study –300-US: doses of 20 or 40 of PANTO, given orally once-a-day were generally safe and well-tolerated. No deaths occurred during this trial. Pt. 30186-001, a 30-y old male, had a drug eruption associated with photosensitivity, an AE which caused withdrawal of this patient from the trial. One patient, randomized to NIZ 150 mg BID reported stomach cramping, while another reported increased dyspepsia. These events resulted in withdrawal of both patients from the trial. There were no significant differences between the PANTO groups and NIZ in the incidence serious AEs or discontinuations because of AEs. Most AEs were minor and resolved upon treatment discontinuation. These data confirmed that the side effect profile of PANTO is as that of other PPIs: the most frequent AE for PANTO was headache and diarrhea. But, in this trial, the incidence of these AEs was not different between PANTO and NIZ. Similarly, the rate of occurrence of treatment-emergent AEs was similar among the three treatment groups. Other than the expected significant increases in serum gastrin (all PPIs, like PANTO, induce hypergastrinemia and these effects are usually dose-dependent and significantly higher than those with H_2-blockers like NIZ), there were no clinically significant changes observed in laboratory screens.

X. OVERALL SUMMARY OF EFFICACY

In support of the claim for pantoprazole efficacy in healing erosive esophagitis, the sponsor submitted results of two pivotal, randomized, multicenter, double-blind, parallel studies: -300-US, a 4-arm trial testing the effect of 3 dose levels of the drug (10, 20 and 40 mg QD) vs a negative control (placebo) and –301-US, a 3-arm study testing the effects of 2 dose levels of the drug (20 and 40 mg QD) vs an adequate positive control (NIZ at the recommended dose of 150 mg BID). From the results of study –300-US, the sponsor concluded that PANTO in doses 10, 20 or 40 mg was significantly more effective than PL in healing lesions and treating secondary symptoms associated with EE. The sponsor noted that the 40-mg dose of PANTO (the recommended dose) provided the greatest healing rates at 4 and 8 weeks and was more effective than the 10-mg and 20-mg doses in the healing of the severe grade 3 or 4 EE lesions. From the results of study – 301-US, the sponsor concluded that PANTO in doses of 20 or 40 mg was significantly more effective than NIZ in treating EE at both 4 and 8 weeks of therapy and that the effectiveness was shown regardless of baseline *H. pylori* status (positive or negative) or disease severity.

The reviewer presented, in Table 3, a summary of the main features of these critical clinical trials and their importance in establishing the efficacy of the drug for the proposed indication. Upon a detailed review of the evidence, the reviewer concluded that both critical trials were well-designed and apparently well-executed. After his assessment, the reviewer agrees with the main conclusion drawn by the sponsor. But important clarifications need to be considered. The clinical response based on EE healing rates, the primary endpoint of efficacy, from the two pivotal trials is depicted in Summary Table 37. In both critical clinical trials, the endoscopically verified healing of all esophageal erosions or ulcerations to grade 1 or less is a direct measure of clinical benefit, to the patient. The secondary efficacy endpoints, the relief of symptoms associated with GERD is also of unique importance to the patient. In Table 37 the emphasis is put on the comparison of the 40 mg QD PANTO dose.
This is the dose proposed by the sponsor and recommended in the proposed labeling. Results with this PANTO dose are contrasted with those seen with the 20 mg QD. Although significantly more efficacious than PL, the response with 10 mg QD was significantly lower than the 40 or even the 20 mg; healing rates with this 10 mg dose of the drug are not included inTable 37.

TABLE 37
NDA 20-987
Overall Summary of Efficacy

Erosive Esophagitis Healing Rates at 4 and 8 Weeks by Treatment Groups for Principal Clinical Trials

Critical Study	PL	PANTO (mg/day) 20	PANTO (mg/day) 40	NIZ (mg BID) 150	Conclusions related to the two dose levels of PANTO, based on statistical significance (superiority)	
I. HEALING RATES AT 4 WEEKS						
-300-US	13.6%	55,1%	72.2%	N/A	20 >[a] PL [<0.001] 20 > 10 [0.022]	40 > PL [<0.001] 40 > 10 [<0.001] 40 > 20 [0.001]
-301-US	N/A	60.0%	64.9%	20.5%	20 > NIZ [<0.001]	40 > NIZ [<0.001] 40 =[b] 20 [N.S.]
Range of Healing		55% - 60%	65% - 72%			
II. HEALING RATES AT 8 WEEKS						
-300-US	32.9%	77.6%	87.9%	N/A	20 > PL [<0.001] 20 > 10 [<0.001]	40 > PL [<0.001] 40 > 10 [<0.001] 40 > 20 [0.015]
-301-US	N/A	73.8%	74.1%	36.6%	20 > NIZ [<0.001]	40 > NIZ [<0.001] 40 = 20 [N.S.]
Range of Healing		74% - 78%	74% - 88%			

Reviewer's Table
N/A = Not applicable
a) = The sign > means that one group is statistically superior to the other
b) = The sign = denotes lack of statistically significant difference between the groups.

The conclusions on the assessment of efficacy (see last 2 columns in Table 37) are now used by the reviewer in an attempt to answer the following 6 questions proposed at the end of section VII. of this review.

[**NOTE:** Overall conclusions on safety are given in the next section of the current review.]

1. Is 40 mg PANTO (the proposed dose) safe and effective?
2. Is 20 mg PANTO safe and effective?
3. Is 40 mg PANTO more effective than 20 mg PANTO for the proposed indication?
4. Is 40 mg PANTO once-a-day more effective than NIZ 150 mg BID?
5. Is 20 mg PANTO once-a-day more effective than NIZ 150 mg BID?
6. Should the claim of PANTO superiority over NIZ be granted on the basis of one study only?

The question of efficacy of PANTO 40 mg once-a-day at 4 weeks is settled by study –300-US (superiority to PL, 10 and even 20 mg PANTO). Efficacy of this dose of PANTO at 4 weeks is supported by the results from study –301-US (superiority to NIZ at the recommended dose of 150 mg BID). The question of efficacy of PANTO 40 mg once-a-day at 8 weeks is also settled by study –300-US (superiority to PL, 10 and 20 mg PANTO). Efficacy of this dose of PANTO at 8 weeks is supported by the results from study –301-US (superiority to NIZ at the recommended dose of 150 mg BID).

The question of efficacy of PANTO 20 mg once-a-day at 4 and 8 weeks is also settled by study –300-US (superiority to PL and 10 mg PANTO) and these results are supported by those from study –301-US (superiority to NIZ at the recommended dose of 150 mg BID).

The question of whether PANTO 40 mg once-a-day is more efficacious than the 20 mg dose is settled by study –300-US where the main comparison group was a negative control (PL). The therapeutic gains when the dose of PANTO was increased from 20 to 40 mg were 17.1% at 4 weeks and 10.3% at 8 weeks. Both therapeutic gains are clinically relevant and statistically significant (p=0.001 and 0.015, respectively). It is, however, true that the superiority of the 40 over the 20 mg PANTO dose is not confirmed in study –301-US, where the comparison group was a positive control (NIZ). There is no plausible explanation for this inconsistency. It is worth noting that the responses with this active comparator in study –301-US (20.5% at 4 weeks and 36.6% at 8 weeks) were somewhat higher than the PL responses in study –300-US (13.6% at 4 weeks and 32.9% at 8 weeks). In conclusion, the 40 mg PANTO is effective. Although the 40 mg is preferred, the 20 mg PANTO is also effective.

> [**NOTE:** The recommended dose currently marketed in Europe is also 40 mg once-a-day.]

The question of whether 40 mg once-a-day PANTO is more effective than the recommended dose of NIZ (150 mg twice-a-day) is settled by study –301-US. This dose of PANTO was very well differentiated from NIZ, with large, clinically impressive therapeutic gains (44.4% at 4 weeks and 37.5% at 8 weeks) and robust results supported by very low p-values (<0.001 for both comparisons). **The robustness of this trial was confirmed by Dr. F. Harrison, our statistician.**

The question of whether 20 mg once-a-day PANTO is more effective than the recommended dose of NIZ (150 mg twice-a-day) is also settled by study –301-US. As the 40 mg, the 20 mg dose was very well differentiated from NIZ, with large, clinically impressive, therapeutic gains (39.5% at 4 weeks and 37.2% at 8 weeks) and robust results supported by very low p-values (<0.001 for both comparisons).

The reviewer believes that claim of superiority of PANTO over NIZ should be granted on the basis of study –301-US only. First, NIZ was used at the recommended dose (for the same indication) of 150 mg BID. Second, the marked differences in healing rates were demonstrated in a well-designed and well-executed trial under conditions that minimized bias. Third, the differences in healing rates are very large: these are considered very meaningful therapeutic gains supported by very robust statistical significance ($p<0.001$) that demonstrate that the chance that these differences were due to random effects were minimal. Fourth, based on what it is known about effectiveness of PPIs and those of H_2 blockers, specifically NIZ, summarized in Section III. of this review, one expects better efficacy with the former than with the latter. Indeed, in study –301-US, healing rate with NIZ at 4 weeks (20.5%) falls between the labeling described 16% (3 weeks) and 21% to 32% (6 weeks); the NIZ healing rate at 8 weeks (36.6%) is close to the labeling described 21% to 32% at 6 weeks and 29% (12 weeks). Statistically, study –301-US did not test whether an effect (superiority of PANTO to NIZ) existed because such an effect can be inferred from a number of considerations, including those mentioned in this review. Study –301-US rather tested **the magnitude of the effect.** The latter was evaluated under a well-designed and well-executed high-quality protocol, where bias was minimized and the results obtained were very robust ($p<0.001$ for all comparisons). Fifth, the superiority of PANTO (both dose levels) over NIZ in comparisons of erosive esophagitis healing, the primary parameter of efficacy is confirmed when effects on symptoms, the secondary parameters of efficacy, are compared. Starting on the first week of therapy, the PANTO 40 mg dose was significantly more efficacious than NIZ in a) the persistent absence of symptoms, b) daytime heartburn, c) nighttime heartburn, d) regurgitation and antacid consumption (use of significantly lower Gelusil tablets in the PANTO 40 mg than the NIZ group). An additional reason to conclude that NIZ is not as good as PANTO in either the healing of esophageal lesions or the relief of symptoms associated with erosive esophagitis is that, in study –301-US, the superiority of PANTO over NIZ was demonstrated not only with 40 mg of the PPI but with 20 mg as well. The reviewer concludes that –301-US fits the requirements of the one study for approval approach. Furthermore, granting superiority of PANTO over NIZ on the basis of results of one trial only is in keeping with the recent regulatory action on rabeprazole (a PPI made approvable recently) in comparison to ranitidine (tested at the recommended dose of 150 mg QID). In that instance, superiority of RABE over RAN is being granted on the basis of one well-designed, well-executed trial where bias was minimized and the differences between the comparator were very meaningful clinically and very robust statistically ($p<0.001$).

XI. OVERALL SUMMARY OF SAFETY

[More details of the overall safety of orally administered pantoprazole are given in the review of the Safety Update.]

These trials (-300-US and –301-US) and other studies, including Phase I evaluations, showed that PANTO, at dose levels of up to 40 mg QD, is safe and well-tolerated. There were no unexpected AEs. Only a few SAEs occurred and these were assessed as unrelated to test medication. Withdrawals due to severe/serious or other AEs were similar with PANTO and comparators (PL in one trial, NIZ 150 mg BID in the other). The most frequently reported AE was headache but in both studies the incidence of this AE was the same between PANTO and comparators (PL in one trial, NIZ in the other). Treatment-emergent AEs were few and mostly mild and transient. No clinical trial showed significant changes in physical examination, heart rate, systolic or diastolic blood pressure, or EKG evaluations. No notable dose-related differences (10 to 20 to 40 mg QD) were found regarding AEs. Minor but inconsistent abnormalities in laboratory parameters, at times statistically significant, were not considered clinically important. In the erosive esophagitis population, the safety and tolerance profile of PANTO 40 mg once-a-day was similar to that of lower doses (20 or 10 mg) of the drug. In both studies, the serum gastrin studies reflected only the dose-related increases expected of a proton pump inhibitor. These increases were higher with all three doses of PANTO than PL in study -301-US and higher than those observed with NIZ in study –301-US. In one study, these increases in median serum gastrin levels were highest with the 40 mg PANTO dose after 8 weeks of treatment whereas in the other, the increases, also with the 40 mg dose, were highest at 4 weeks. In both trials, the increases in median serum gastrin were higher in patients who were concomitantly infected with *H. pylori* than in those that were *H. pylori* [-].

In conclusion, the results of these two trials in NDA 20-987, very convincingly demonstrate the great superiority of pantoprazole 40 mg once-a-day over placebo (in one study) and over the approved dose/regimen of nizatidine (in the other), in the healing of esophageal lesions and the relief of symptoms associated with GERD. This dose of pantoprazole is safe and well-tolerated. It is also worth noting that in a clinical pharmacology dose-response study, the 40-mg oral dose of pantoprazole markedly inhibited gastric acidity (sponsor's Ref. 17); pharmacodynamically, there were no significant differences between 40-mg and higher doses, such as 80-mg. Furthermore, acid inhibition was significantly higher after the 40-mg dose than after the 20-mg dose of pantoprazole. Thus, from the pharmacodynamic perspective, the 40-mg dose is expected to be associated with better or at least the same efficacy than that seen with the 20-mg dose of pantoprazole.

XII. RECOMMENDATIONS FOR REGULATORY ACTION

1. It is recommended to approve a regimen of 40 mg once-a-day of pantoprazole for the short-term treatment (— 8 weeks) of erosive esophagitis and the relief of daytime and nighttime heartburn and regurgitation associated with gastroesophageal reflux disease (GERD).

   This recommendation is based on results of two well-designed, well-controlled and apparently well-executed trials. Study –300-US [comparing three dose levels of the drug (10, 20 or 40 mg/day) to PL] and –301-US [comparing 20 or 40 mg PANTO to NIZ].

2. Superiority of pantoprazole over nizatidine for healing of esophagitis and relief of GERD symptoms may be claimed.

   This recommendation is based on results of study –301-US, a well-designed and apparently well-executed trial where the active comparator was the recommended dose/regimen of nizatidine (150 mg BID).

3. Matters related to the proposed labeling are being addressed separately.

April 16, 1999

/S/

Hiugo E. Gallo-Torres, M.D., Ph.D.

cc:
NDA 20-987
HFD-180
HFD-180/LTalarico /S/ 4-19-99
HFD-180/HGallo-Torres
HFD-181/PM
HFD-180/JChoudary
HFD-180/EDuffy
r/d 3/16/99 jgw
f/t 4/15/99 jgw

APPEARS THIS WAY
ON ORIGINAL