MYLANTA™ Double Strength (calcium carbonate-magnesium hydroxide) pink cherry-flavored antacid tablets were provided as "rescue" medication in the event that during the double-blind home assessment period, patients had continuing or recurrent heartburn between 1 and 8 hours postdose for which they felt additional relief was essential. Patients were discouraged from using rescue medication in the first hour after taking study medication.

Comparison of Study Design to Protocol 110

Protocol 110, previously submitted, was identical in design and execution with similar one week run-in-period and two week double-blind four-dose trial therapy periods, inclusion and exclusion criteria, primary objective, efficacy endpoints and safety parameters. The number of patients participating was slightly smaller, approximately 300 per treatment group, and 600 patients and 2400 episodes involved in the comparisons of any two treatments.

Prior and Concomitant Medication(s)/Treatment(s)

The following restrictions on prior or concomitant medications applied:

From 4 Weeks Prior

- Omeprazole or lansoprazole were not permitted within 4 weeks of the baseline run-in period until completion of the double-blind period.

From 1 Week Prior

- Prescription sucralfate, nizatidine, cimetidine, ranitidine, cisapride, famotidine, misoprostol, and metoclopramide and any form of oral tetracycline were not permitted.
- Orally administered corticosteroids, anticholinergics, tricyclic antidepressants, anticoagulants, and antineoplastics were prohibited.
- OTC H2-receptor antagonists were permitted up to Visit 1.

General Restrictions

Antacids were permitted only after all study medication had been used, i.e.. 30 doses of baseline antacid had been consumed during the run-in period, or all 4 doses of double-blind study medication had been taken during the double-blind period, except in the case of rescue medication as per protocol.

Acetaminophen could have been taken for minor discomforts, and aspirin could have been taken at low doses (≤325 mg/day) for prophylactic anticoagulation.

If other conditions emerged that required drug therapy during this study, those conditions and any concomitant prescribed medication were recorded on the workbooks.

Diet/Activity/Other

Patients were not permitted to eat or drink for the first hour post-dose during both the run-in and double-blind periods. The time of any food or drink consumption during the 8-hour (double-blind weeks) assessment period was recorded on the diary card.

If the patient was a smoker, smoking was permitted during the assessment period according to the patient's normal habits.

The patient had to remain awake and not lie down for the first hour post-dose.

Rescue Medication

Patients were informed that rescue medication was available between 1 and 8 hours post-dose, although use within 1 hour of taking study medication was discouraged. One MYLANTA^{TM} Double Strength antacid tablet was administered, as rescue medication for continued or recurrent heartburn symptoms for which the patient felt additional relief was essential. Additional tablets may have been taken if needed. If rescue medication was used, the time it was taken was recorded on the diary cards. The sponsor provided commercially available MYLANTA^{TM} Double Strength antacid tablets to each study site.

Clinical Observations and Laboratory Measurements

Clinical observations (events/actions and timing) for each of the three study visits for protocol 127 are listed in Table 3, for the run-in period in Table 4 and for the double-blind home assessment period in Table 5.

Table 3
Study Visits

	Visit 1	Visit 2†	Visit 3‡
Medical history	X		
Evaluation of inclusion/exclusion criteria	X		
Informed consent	X		
Review home assessment/diary card instructions	X	X	
Dispense run-in week medication, diary card, timer	X		
Dispense double-blind medication and diary card		X	
Monitor prior/concomitant medications	X	X	X
Review diary card		X	X
Record overall global assessment			X
Adverse experience monitoring		X	X

† Visit 2 occurred within 5 days of completion of run-in week.
‡ Visit 3 occurred within 5 days of completion of 2-week double-blind period.

Table 4

Run-In Period Home Assessment†

Event/Action	Timing
Spontaneous episode of heartburn	0 hour
Assess baseline heartburn	0 hour
Take study medication	0 hour
Record relief assessments at 15-minute intervals	0 to 1 hour postdose (four ratings)

† Home assessments occurred within 7 days of Visit 1.

Table 5

Double-Blind Period Home Assessment†

Event/Action	Timing
Spontaneous episode of heartburn	0 hour
Assess baseline heartburn	0 hour
Take study medication	0 hour
Record relief assessments at 15-minute intervals	0 to 1 hour postdose (four ratings)
Record relief assessments at 60-minute intervals	1 through 8 hours postdose
Record use of rescue medication	0 to 8 hours postdose

† Home assessments occurred within 14 days of Visit 2.

Samples of the multiple-dose dairy cards utilized by the patients can be seen in Appendix 1.

Evaluation Criteria

Patients were provided with a diary card to record information during the home assessment periods.

Heartburn Severity

Patients rated heartburn severity immediately before taking study drug during both the baseline run-in and double-blind periods. Patients used the following 3-point scale:

Grade		Severity
1	=	Mild
2	=	Moderate
3	=	Severe

Heartburn Relief

Patients answered the following question at 15-minute intervals for 1 hour post-dose, and at 2 to 8 hours post-dose (double-blind period):

"Do you have adequate relief of your heartburn symptoms at this time?"

1 - Yes

2 = No

3 = Sleeping

The sleeping response was not an option until 2 hours post-dose.

Overall Global Evaluation of Treatment Efficacy

At the follow-up visit (Visit 3), patients evaluated overall treatment efficacy. Patients answered the question, "How well did the test medication control your heartburn?" using the following scale:

Grade	Rating
4 =	Excellent
3 =	Good
2 =	Fair
1 =	Poor
0 =	Ineffective

Use of Open-Label Rescue Medication

Patients were allowed to use rescue medication to treat continuing or recurrent heartburn symptoms for which they felt additional relief was essential between 1 and 8 hours post-dose. Patients were discouraged from using rescue medication within 1 hour of taking study medication. When patients used rescue medication, they noted the time of the administration.

Safety Measurements

Adverse experiences were recorded throughout the study.

Evaluating and Recording Adverse Experiences

Adverse experiences were monitored throughout this study and such events were recorded at each examination on the Adverse Experience Case Report Forms.

An adverse experience was defined as any unfavorable and unintended change in the structure, function, or chemistry of the body, or worsening of a preexisting condition, temporally associated with any use of a trial drug whether or not considered related to the use of the product.

The investigator evaluated all adverse experiences as to:

- Maximum intensity:
  - Mild (awareness of sign or symptom, but easily tolerated);
  - Moderate (discomfort enough to cause interference with usual activity);
  - Severe (incapacitating with inability to work or do usual activity).
- Seriousness
- Duration
- Action taken (whether or not the adverse experience caused the patient to discontinue the test drug); and

- Relationship to test drug (whether or not the test drug caused the adverse experience to be graded as):
  - 5 = Definitely (unquestionable relationship)
  - 4 = Probably (relationship is likely)
  - 3 = Possibly (relationship may exist)
  - 2 = Probably not (relationship is not likely)
  - 1 = Definitely not (no relationship)

The outcomes of all adverse reactions were followed and recorded. Information concerning the occurrence of adverse experiences was recorded on the patient's case report "AE" (Adverse Experience) Form.

3. STATISTICAL PLANNING AND ANALYSIS:

As in Study 110, time to adequate relief and duration of adequate relief were analyzed using complex generalized estimating equations (GEE) for ordered categorical outcomes. This complex method accounted for the intra-patient correlation resulting from analyzing multiple episodes for each patient. The final model used in making comparisons among the treatment groups included factors for treatment group, investigator site. and a covariate for average baseline heartburn severity. Treatment-by-investigator and treatment-by-baseline heartburn severity interactions were evaluated by constructing the appropriate Wald chi-square statistic. For the analysis of time to adequate relief, patient data consisted of the number of episodes with adequate relief first occurring at each of thc following 6 time points: 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, and >2 hours. For the analysis of duration of adequate relief, patient data consisted of the number of episodes with adequate relief sustained through each of the following 6 time points: $\geq$7 hours, 6 to 7 hours, 5 to 6 hours, 4 to 5 hours, <4 hours, and "no onset of adequate relief." Because both primary treatment comparisons (famotidine/antacid combination versus famotidine 10 mg for onset; famotidine/antacid combination versus antacid 21 mEq for duration) were required to be statistically significant at α=0.050, no adjustments for multiple comparisons were made.

With 400 patients per treatment group, 800 patients in each comparison, 3200 episodes were involved in the comparison of any 2 treatments. Assuming α=0.050 (two-tailed) and an intraclass correlation among episodes within a patient of p=0.8, these sample sizes provided greater than 98% power to detect a difference of 0.10 in the probability of adequate relief at 30 minutes (0.46 for famotidine/antacid combination versus 0.36 for famotidine l0 mg FCT) and greater than 99% power to detect a difference of 0.10 in the probability of duration of adequate relief $\geq$6 hours (0.72 for famotidine/antacid combination versus 0.62 for antacid 21 mEq). The power associated with these treatment comparisons increases as the intraclass correlation decreases.

Examples of the many assumptions and complexity of the statistical analyses follows. Mean onset and duration were calculated by assigning these numeric values of the onset and duration analyses and standardizing to 4 episodes (range of possible values is 0 to 20). For each of the primary parameters, the outcome for a patient was a 6-element vector consisting of numbers of that patient's episodes falling into the six result categories. This vector had a multinomial distribution with covariance matrix inflated by a factor reflecting the number of episodes and the strength of the intrapatient correlation.

Data displays for the three ordered categorical GEE parameters (time to adequate relief, duration of adequate relief, and time to rescue medication) present numbers of episodes and cumulative percentages for each of the 6 time points. The cumulative percentages displayed in these tables are "patient-based" rather than "episode-based." In other words, the displayed percentages are based on the proportion of episodes for each time point within a patient averaged over all patients in the treatment group. This adjusts for the fact that not all patients had the same number of total episodes and is the reason why the cumulative percent cannot be derived by dividing the number of episodes by the total episodes. In a similar fashion, data displays for the binary GEE parameter ("successfully treated" episodes) display percentages that are "patient-based" rather than "episode-based." Overall global assessment was analyzed using a logistic regression model for ordered categorical data. Using this model, the ordinal data are assumed to represent ranges from an underlying continuous distribution. and maximum likelihood estimation is used to determine the location of this continuous distribution as a function of the independent variables. The final model used in making comparisons among the treatment groups included factors for treatment group and investigator site. Treatment-by-investigator interactions were evaluated by constructing the appropriate Wald chi-square statistic. The proportion of patients who reported a good or excellent global assessment was analyzed using a logistic regression model for binary data. This model is a special case of the logistic regression model for ordered categorical data described above.

The natural measure of a treatment difference in logistic regression models is the odds-ratio, because a shift in the logistic distribution corresponds exactly to the odds-ratio. The odds-ratio for Treatment A relative to Treatment B is the ratio of the odds of a random patient having a better response on A to the odds of a random patient having a better response on B. In the simplest case of a binary outcome, if the probability of a successful outcome on Treatment A is 0.6 and the probability of a successful outcome on Treatment B is 0.2, then the odds of a successful outcome on A is 6 to 4. the odds of a successful outcome on B is 2 to 8. and the odds ratio is 6.0.

In conclusion the sponsor suggested that odds-ratios appearing in the Efficacy section with values >1 favor the first-listed treatment group of the pairwise comparison and odds-ratios <1 favor the second-listed treatment group. If the proportional odds assumption was violated, the pattern of the treatment effect across the cutpoints of the parameter was examined. If the treatment effect varied in magnitude but not in direction, the logistic regression model produced

an estimate of the treatment effect "averaged" across the cutpoints, i.e.. the odds ratio between treatments was the common odds ratio across the adjacent categories.

Additional analyses were performed to determine the impact of demographic characteristics (age, gender, and race) on treatment effect. Fisher's exact test was used to compare treatment groups with respect to the incidence of clinical adverse experiences. All statistical tests were two-tailed and were performed at the 5% significance level. All p-values were rounded to three decimal places and statistical significance declared if the rounded p-value was less than or equal to 0.050.

Patient Population

Thirty-two investigators screened a total of 2429 patients who reported for the run-in phase of the study. A total of 1651 patients were randomized to one of the four treatment groups. The most frequent reason for patients not qualifying for the double-blind phase was inadequate heartburn during the run-in period. There were 410 patients randomized to the famotidine-antacid combination group, 414 to the famotidine 10-mg FCT group, 419 to the antacid 21 mEq group, and 408 patients randomized to the placebo group. Six hundred fifty-five (40%) of the patients were male. The patients' ages ranged from 18 to 90 for males and 18 to 82 for females. For a breakdown of age ranges by gender and treatment group for the 1640 patients in the safety population, see Table 6.

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Table 6
Protocol 127

Mean Age by Gender and Treatment Group
Safety Population (N=1640)

Treatment Group	Gender	n	Mean	Median	Range
FACT	Male	168	44.3	44.5	18 to 90
	Female	242	46.2	45.0	18 to 82
	Total	410	45.4	45.0	18 to 90
FAM 10-mg FCT	Male	167	47.8	47.0	19 to 80
	Female	244	45.2	44.5	18 to 82
	Total	411	46.3	45.0	18 to 82
Antacid 21 mEq	Male	148	44.7	42.0	19 to 78
	Female	266	44.0	43.0	18 to 79
	Total	414	44.3	43.0	18 to 79
Placebo	Male	170	46.7	44.0	20 to 85
	Female	235	46.2	45.0	18 to 81
	Total	405	46.4	45.0	18 to 85

FACT = Famotidine/antacid combination; FAM = Famotidine.

The treatment groups appeared similar with regard to all baseline characteristics. The most frequently reported secondary diagnoses were hypertension and headache. The most common prior drug therapies in each treatment group were antacids (calcium carbonate and dihydroxyaluminum sodium carbonate. A total of 1298 patients (79%) took at least 1 concomitant therapy during the study. The most common concomitant therapy in each treatment group was the antacid provided as rescue medication (magnesium hydroxide/calcium carbonate), 51%-69%.

Accounting for Patients in the Study

A total of 1651 patients were randomized to 1 of the 4 treatment groups. Of this total, 1489 (90%) completed the study. Table 7 presents the number (%) of patients who entered, completed, and discontinued the study.

Table 7
Protocol 127
Patient Accounting for All Randomized Patients (N=1651)

	FACT	Famotidine 10-mg FCT	Antacid 21 mEq	Placebo	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
Total randomized	410	414	419	408	1651
Completed study	377 (92.0)	387 (93.5)	368 (87.8)	357 (87.5)	1489 (90.2)
Discontinued study	33 (8.0)	27 (6.5)	51 (12.2)	51 (12.5)	162 (9.8)
Clinical AE	0 (0.0)	0 (0.0)	3 (<1)	4 (1.0)	7 (<1)
Lost to follow-up	3 (<1)	5 (1.2)	6 (1.4)	5 (1.2)	19 (1.2)
Protocol deviation	0 (0.0)	1 (<1)	3 (<1)	0 (0.0)	4 (<1)
Withdrew	0 (0.0)	1 (<1)	0 (0.0)	1 (<1)	2 (<1)
Uncooperative	0 (0.0)	0 (0.0)	0 (0.0)	1 (<1)	1 (<1)
Diary not returned	0 (0.0)	0 (0.0)	1 (<1)	0 (0.0)	1 (<1)
Therapy ineffective	0 (0.0)	0 (0.0)	0 (0.0)	1 (<1)	1 (<1)
Took <4 doses	30 (7.3)	18 (4.3)	35 (8.4)	34 (8.3)	117 (7.1)
Family situation	0 (0.0)	0 (0.0)	0 (0.0)	2 (<1)	2 (<1)
Did not medicate	0 (0.0)	2 (<1)	3 (<1)	3 (<1)	8 (<1)

Accounting for Patients in the Analysis

Safety Population/All-Patients-Treated Approach/Per-Protocol Approach

Of the 1651 patients randomized, 11 patients did not medicate and were not included in the safety or efficacy analyses (stated reasons for discontinuing: did not medicate--8 patients; protocol deviation--3 patients). The remaining 1640 patients comprise the safety population and include 1621 patients who took at least 1 dose of study medication (including 1 patient who discontinued due to a protocol deviation) and 19 patients who were lost to follow-up. The lost to follow-up patients are included in safety analyses as if they had dosed and reported no adverse experiences. Of the 1621 patients who dosed, 3 patients were excluded from the all-patients-treated population. Therefore no efficacy data were available. The remaining 1618 patients were used for the all-patients-treated analyses (406 in the famotidine/antacid combination group, 406 in the famotidine 10-mg FCT group, 407 in the antacid 21 mEq group, and 399 in the placebo group). A memo regarding protocol violators stated that the 13 patients who treated only 1 episode of heartburn in the study would be excluded from the GEE analyses. However, these patients have been included in all analyses where data were available.

In the per-protocol approach, serious protocol violators were excluded. Forty-nine of the patients (3.0% of the all-patients-treated population) were considered serious protocol violators. Appendix 2 provides a brief description of the protocol violations for these patients.

4. EFFICACY

The efficacy analyses presented in this report are based on 1618 patients who treated, and provided efficacy data for a total of 6281 episodes. Of these episodes, 89.6% occurred between the hours of 7:01 AM and 11 PM with the remaining 10.4% occurring during the night. The hourly intervals with the greatest number of episodes were 1:01 PM to 2 PM (6.8%), 6:01 PM to 7 PM (7.6%), 7:01 PM to 8 PM (7.8%) and 8:01 PM to 9 PM (6.9%).

Treatment-by-Investigator and Treatment-by-Demographic Factor Interactions

Many of the investigator sites had relatively small sample sizes. No site had more than 30 patients per treatment group and 20 of the 32 sites (63%) had less than 15 patients in each of the 4 treatment groups. Notwithstanding the variability among investigators that is apparent in these displays, the famotidine/antacid combination group had a consistently earlier mean onset of action than the non antacid groups (famotidine 10-mg FCT and placebo). Specifically, the famotidine/antacid combination group had an earlier mean onset of action than the famotidine 10-mg FCT group at 24 of the 32 investigator sites. Also, the famotidine/antacid combination group consistently had a longer mean duration of effect than the non-famotidine groups (antacid 21 mEq and placebo). Specifically, the famotidine/antacid combination group had a longer mean duration of effect than the antacid 21-mEq group at 23 of the 32 investigator sites. These results imply interactions that are quantitative in nature. For global assessment, there was no evidence of a treatment-by-investigator interaction ($p>0.050$), for either the ordered categorical or the binary end point.

For both primary efficacy endpoints, there was no evidence of a treatment-by-factor interaction for the demographic characteristics of gender and race. However, the famotidine/antacid combination group had an earlier mean onset of action for the older than 44 age group than for the 44 or younger age group. For both primary efficacy endpoints, there was no evidence of a treatment-by-baseline heartburn severity interaction ($p>0.050$).

Onset

The primary hypothesis regarding onset of treatment effect was that famotidine/antacid combination tablet produced a faster time to adequate relief than famotidine 10-mg FCT. The data used to address this question were the number of episodes within each patient with adequate relief first occurring at each of the following 6 time points: 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours and >2 hours. The results of the all-patients-treated analysis of these data are displayed in Table 8 and Figure 1.

Table 8
Study MRL Protocol 127
Onset Data
NUMBER AND CUMULATIVE % EPISODES ADEQUATELY RELIEVED
ALL-PATIENTS TREATED APPROACH (N=1618)

Adequate Relief At:	FACT n=406 Tot Eps†=1585		FAMOTIDINE 10-mg FCT n=406 Tot Eps=1598		ANTACID 21 mEQ n=407 Tot Eps=1565		PLACEBO n=399 Tot Eps=1533	
	n	cum %†	n	cum %	n	cum %	n	cum %
15 mins	540	33.7	430	27.3	508	32.4	386	25.4
30 mins	291	52.4	304	46.6	259	48.8	265	42.7
45 mins	284	70.5	279	63.8	281	66.9	291	61.7
60 mins	188	82.2	170	74.3	188	78.7	187	73.7
120 mins	72	86.8	91	79.9	81	84.0	74	78.5
>120 mins	210	100.0	324	100.0	248	100.0	330	100.0

† Eps = episodes
‡ Cumulative percentages are "patient-based."

Based on sponsor's table 13

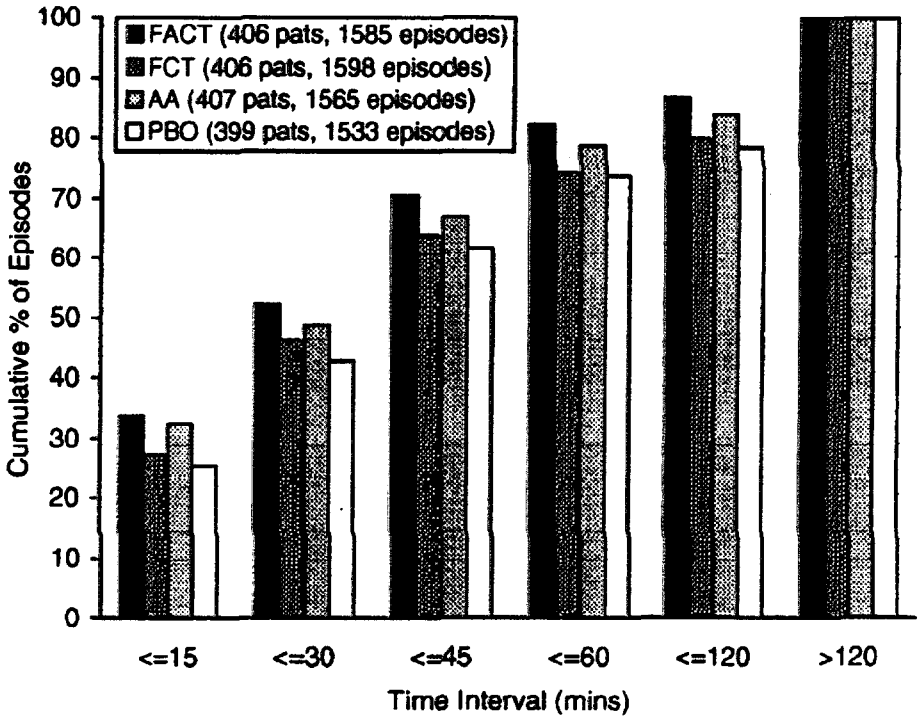
Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
FACT vs. FAM 10-mg FCT	1.42 (1.17, 1.73)	12.10	0.001
FACT vs. AA 21 mEq	1.18 (0.96, 1.45)	2.52	0.113
FACT vs. Placebo	1.59 (1.31, 1.94)	21.16	<0.001
FAM 10-mg FCT vs. Placebo	1.12 (0.92, 1.36)	1.34	0.248
AA 21 mEq vs. Placebo	1.35 (1.10, 1.65)	8.54	0.003
FAM 10-mg FCT vs. AA 21 mEq	0.83 (0.68, 1.01)	3.29	0.070

The distribution of episodes (patient-based) for the famotidine/antacid combination group is shifted towards the earlier time points relative to each of the two non antacid-containing treatment groups. Also, the distribution of episodes for the antacid 21 mEq group shifted towards the earlier time points relative to the placebo group. The odds-ratios indicate that heartburn episodes for famotidine/antacid combination patients were 1.42 and 1.59 times more likely to achieve adequate relief at an earlier time point than episodes for famotidine 10-mg FCT and placebo patients, respectively ($p=0.001$ and $p<0.001$). The odds-ratio indicates that heartburn episodes for antacid 21-mEq patients were 1.35 times more likely to achieve adequate relief at an earlier time point than episodes for placebo patients ($p=0.003$).

The results for the per-protocol analysis are consistent with the all-patients-treated approach.

Figure 1

Onset Data
All-Patients-Treated Approach (N=1618)



Duration

The primary hypothesis regarding duration of treatment effect was that the famotidine/antacid combination tablet produced a longer duration of adequate relief than antacid 21 mEq. The data used to address this question were the number of episodes with adequate relief sustained through each of the following 6 time points: ≥7 hours, 6 hours, 5 hours, 4 hours, <4 hours, and "no onset of adequate relief." The results of the all-patients-treated analysis of these data are displayed in Table 9 and Figure 2.

Table 9
Study MRL Protocol 127
Duration Data
NUMBER AND CUMULATIVE % EPISODES ADEQUATELY RELIEVED
ALL-PATIENTS TREATED APPROACH (N=1618)

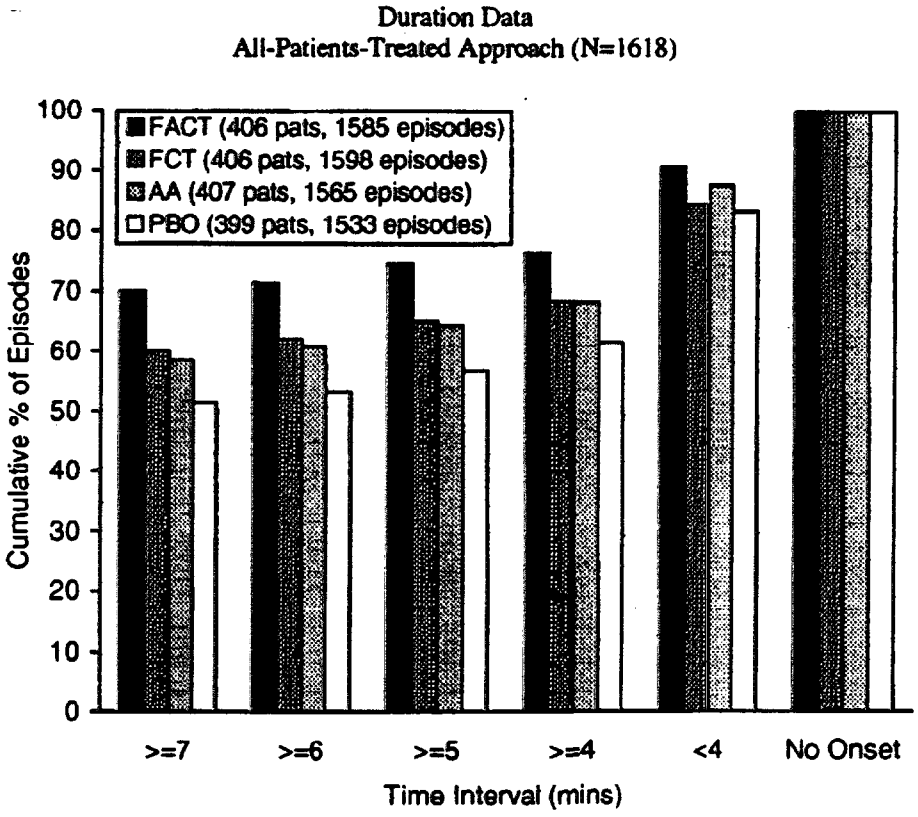
Adequate Relief For:	FACT n=406 Tot Eps†=1585		FAMOTIDINE 10-mg FCT n=406 Tot Eps=1598		ANTACID 21 mEQ n=407 Tot Eps=1565		PLACEBO n=399 Tot Eps=1533	
	n	cum %†	n	cum %	n	cum %	n	cum %
≥ 7 Hrs	1107	70.0	960	60.0	909	58.5	790	51.4
6 Hrs	22	71.3	35	62.1	37	60.7	27	53.2
5 Hrs	49	74.4	46	65.0	58	64.3	54	56.8
4 Hrs	31	76.3	52	68.4	63	68.2	71	61.4
< 4 Hrs	225	90.5	253	84.4	305	87.6	334	83.3
No Onset	151	100.0	252	100.0	193	100.0	257	100.0

† Eps = episodes
‡ Cumulative percentages are "patient-based."

Based on sponsor's Table 14

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
FACT vs. FAM 10-mg FCT	1.57 (1.29, 1.92)	19.84	<0.001
FACT vs. AA 21 mEq	1.60 (1.31, 1.95)	21.91	<0.001
FACT vs. Placebo	2.15 (1.77, 2.62)	59.81	<0.001
FAM 10-mg FCT vs. Placebo	1.37 (1.14, 1.65)	11.12	0.001
AA 21 mEq vs. Placebo	1.35 (1.12, 1.62)	10.23	0.001
FAM 10-mg FCT vs. AA 21 mEq	1.02 (0.84, 1.23)	0.03	0.855

Figure 2



The distribution of episodes (patient-based) for the famotidine/antacid combination shifted towards the later time points relative to each of the other 3 treatment groups. Also, the distribution of episodes for famotidine 10-mg FCT shifted towards the later time points relative to placebo. The odds-ratio indicates that heartburn episodes for famotidine/antacid combination patients were 1.60 times more likely to maintain adequate relief at a later time point than episodes for antacid 21-mEq patients ($p<0.001$). The odds-ratios indicate that episodes for famotidine/antacid combination patients were 1.57 and 2.15 times more likely to maintain adequate relief at a later time point than episodes for famotidine 10-mg FCT and placebo patients, respectively ($p<0.001$ for both). The odds-ratio indicated that episodes for famotidine 10-mg FCT patients were 1.37 times more likely to maintain adequate relief at a later time point than episodes for placebo patients ($p=0.001$). The results for the per-protocol analysis are consistent with the all-patients-treated approach.

Proportion of Episodes "Successfully Treated" for Onset and Duration

The results are given in Table 10 for the analysis of the proportion of episodes "successfully treated" for both onset and duration. Four different time points (15, 30, 45, and 60 minutes post-dose) were used to determine whether the patient satisfied the "onset" portion of the definition. Specifically, an episode was considered "successfully treated" if the patient reported adequate relief at 15, 30, 45, or 60 minutes after dosing that was sustained through 8 hours post-dose and required no rescue medication.

Patients in the famotidine/antacid combination group had a higher percentage of "successfully treated" episodes than patients in the other 3 groups. Twenty-six percent of the heartburn episodes treated with famotidine/antacid combination were "successfully treated" by 15 minutes and 63% were "successfully treated" by 1 hour compared to 14% by 15 minutes and 44% by 1 hour on placebo.

Table 10
Study MRL Protocol 127
Successfully Treated (for Onset and Duration) Data
(Adequate Relief at 15, 30, 45, or 60 Minutes that Lasts Through 8 Hours)
NUMBER AND CUMULATIVE % EPISODES ADEQUATELY RELIEVED
ALL-PATIENTS TREATED APPROACH (N=1618)

Adequate Relief At:	FACT n=406 Tot Eps†=1585		FAMOTIDINE 10-mg FCT n=406 Tot Eps=1598		ANTACID 21 mEQ n=407 Tot Eps=1565		PLACEBO n=399 Tot Eps=1533	
	n	cum %†	n	cum %	n	cum %	n	cum %
15 Min	420	26.2	283	17.9	294	18.9	209	13.8
30 Min	640	40.4	503	31.6	458	29.5	386	25.2
45 Min	847	53.6	689	43.2	649	41.6	574	37.4
60 Min	990	62.6	821	51.4	785	50.2	678	44.0

† Eps = episodes
‡ Cumulative percentages are "patient-based."

Based on sponsor's table 15

Adequate Relief at:	Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
15 mins	FACT vs. FAM 10-mg FCT	1.69 (1.30, 2.20)	15.42	<0.001
	FACT vs. AA 21 mEq	1.61 (1.24, 2.08)	12.83	<0.001
	FACT vs. placebo	2.34 (1.79, 3.07)	38.01	<0.001
	FAM 10-mg FCT vs. placebo	1.38 (1.05, 1.83)	5.22	0.022
	AA 21 mEq vs. placebo	1.46 (1.11, 1.92)	7.17	0.007
	FAM 10-mg FCT vs. AA 21 mEq	0.95 (0.73, 1.24)	0.15	0.699
30 mins	FACT vs. FAM 10-mg FCT	1.52 (1.22, 1.88)	14.15	<0.001
	FACT vs. AA 21 mEq	1.71 (1.37, 2.13)	22.31	<0.001
	FACT vs. placebo	2.13 (1.69, 2.67)	42.04	<0.001
	FAM 10-mg FCT vs. placebo	1.40 (1.12, 1.76)	8.73	0.003
	AA 21 mEq vs. placebo	1.25 (0.99, 1.57)	3.51	0.061
	FAM 10-mg FCT vs. AA 21 mEq	1.13 (0.91, 1.40)	1.14	0.286
45 mins	FACT vs. FAM 10-mg FCT	1.56 (1.28, 1.90)	19.10	<0.001
	FACT vs. AA 21 mEq	1.69 (1.39, 2.06)	27.22	<0.001
	FACT vs. placebo	2.03 (1.66, 2.48)	48.29	<0.001
	FAM 10-mg FCT vs. placebo	1.30 (1.07, 1.59)	6.75	0.009
	AA 21 mEq vs. placebo	1.20 (0.98, 1.47)	3.25	0.071
	FAM 10-mg FCT vs. AA 21 mEq	1.09 (0.89, 1.32)	0.67	0.415
60 mins	FACT vs. FAM 10-mg FCT	1.60 (1.31, 1.95)	21.71	<0.001
	FACT vs. AA 21 mEq	1.70 (1.39, 2.07)	27.47	<0.001
	FACT vs. placebo	2.19 (1.80, 2.68)	59.24	<0.001
	FAM 10-mg FCT vs. placebo	1.37 (1.13, 1.67)	9.83	0.002
	AA 21 mEq vs. placebo	1.29 (1.06, 1.57)	6.47	0.011
	FAM 10-mg FCT vs. AA 21 mEq	1.06 (0.87, 1.29)	0.35	0.551

The odds-ratios indicate that heartburn episodes for famotidine/antacid combination patients were between 1.52 and 1.69 times more likely to be "successfully treated" than episodes for famotidine 10-mg FCT patients ($p<0.001$). Likewise, heartburn episodes for famotidine/antacid combination patients were between 1.61 and 1.71 times more likely to be "successfully treated" than episodes for antacid 21-mEq patients ($p<0.001$) and between 2.03 and 2.34 times more likely to be "successfully treated" than episodes for placebo patients ($p<0.001$).

Global Evaluation

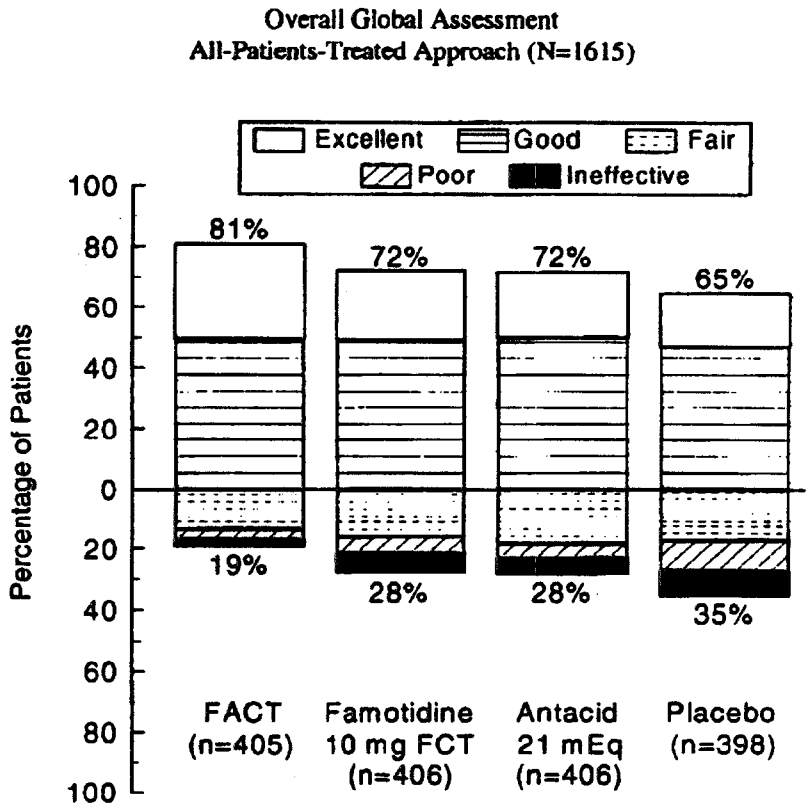
At the end of the study period, patients returned to the clinic and were asked to assess their overall global response to treatment using a 5-point scale. Table 11 (sponsor's Table 16) and Figure 3 display the results for the analysis of this overall global assessment of treatment efficacy. Compared to famotidine 10-mg FCT (72%), antacid 21 mEq (72%) and placebo (65%), a significantly greater proportion of patients receiving famotidine/antacid combination (81%) reported a good or excellent global assessment ($p\leq0.004$). These differences were also statistically significant ($p<0.001$) when all categories of global assessment were analyzed. The odds-ratios for all categories indicate that famotidine/antacid combination patients were 1.59, 1.65 and 2.36 times more likely to report a more favorable

global assessment than famotidine 10-mg FCT, antacid 21-mEq, and placebo patients, respectively. In addition, both famotidine 10-mg FCT and antacid 21-mEq patients reported significantly more favorable global assessments than placebo patients ($p \leq 0.016$ and $p \leq 0.024$, respectively).

Table 11
Study MRL Protocol 127
Overall Global Assessment of Efficacy
NUMBER AND CUMULATIVE %
ALL-PATIENTS TREATED APPROACH (N=1615)

	Famotidine 40-mg FCT (n=405)		Famotidine 10-mg FCT (n=406)		Antacid 21 mEq (n=406)		Placebo (n=398)	
	n	(cum %)	n	(cum %)	n	(cum %)	n	(cum %)
Excellent	126	(31.1)	93	(22.9)	88	(21.7)	70	(17.6)
Good	201	(80.7)	200	(72.2)	203	(71.7)	187	(64.6)
Fair	56	(94.6)	66	(88.4)	75	(90.1)	70	(82.2)
Poor	13	(97.8)	22	(93.8)	19	(94.8)	39	(92.0)
Ineffective	9	(100.0)	25	(100.0)	21	(100.0)	32	(100.0)

Figure 3



Because the Score test of the proportional odds assumption was statistically significant for global evaluation ($p<0.001$), the pattern of the treatment effect across the cutpoints (excellent, good, fair, poor, ineffective) was examined. For the treatment differences that were statistically significant, the treatment effect varied in magnitude but not in direction across the cutpoints, i.e.. the cumulative odds ratios by cutpoint were all >1 in favor of famotidine/antacid combination. The odds-ratio for each treatment comparison presented in Table 11 is therefore the common odds-ratio across the adjacent categories.

Proportion of Episodes Requiring Rescue Medication

The results are given in Table 12 (sponsor's Table 17) for the analysis of the proportion of episodes requiring rescue medication during the 8 hours post-dose. The number of episodes within each patient that required the use of rescue medication are summarized using 6 categories: ≤1 hour, ≤2 hours, ≤4 hours, ≤6 hours, ≤8 hours, and no rescue needed.

Table 12
Study MRL Protocol 127
NUMBER AND CUMULATIVE % EPISODES Requiring Rescue Medication
ALL-PATIENTS TREATED APPROACH (N=1618)

Use of Rescue Medication	FACT n=406 Tot Eps†=1585		FAMOTIDINE 10-mg FCT n=406 Tot Eps=1598		ANTACID 21 mEQ n=407 Tot Eps=1565		PLACEBO n=399 Tot Eps=1533	
	n	cum %†	n	cum %	N	cum %	n	cum %
≤1 hour	34	2.2	72	4.4	60	3.9	72	4.7
≤2 hour	104	8.7	168	14.8	125	12.2	143	13.9
≤4 hour	117	15.9	143	23.7	196	24.5	228	29.1
≤6 hour	80	20.9	95	29.8	113	31.5	158	39.2
≤8 hour	40	23.4	66	33.9	75	36.1	56	42.9
No rescue	1210	100.0	1054	100.0	996	100.0	876	100.0

† Eps = episodes
‡ Cumulative percentages are "patient-based."

Based on sponsor's table 17

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
FACT vs. FAM 10-mg FCT	1.70 (1.38, 2.09)	25.45	<0.001
FACT vs. AA 21 mEq	*1.80 (1.47, 2.21)*	*32.14*	*<0.001*
FACT vs. placebo	2.34 (1.92, 2.85)	69.62	<0.001
FAM 10-mg FCT vs. placebo	1.37 (1.13, 1.67)	10.27	0.001
AA 21 mEq vs. placebo	1.30 (1.07, 1.57)	7.26	0.007
FAM 10-mg FCT vs. AA 21 mEq	1.06 (0.87, 1.29)	0.31	0.580

Patients in the famotidine/antacid combination group had a lower percentage of episodes that required the use of rescue medication than patients in the other 3 groups. Twenty-three percent of the heartburn episodes treated with famotidine/antacid combination required the use of rescue medication during the 8-hour post-dose period compared to 34% for famotidine 10-mg FCT, 36% for antacid 21 mEq, and 43% for placebo. The odds-ratios indicate that episodes for famotidine/antacid combination patients were 1.70, 1.80 and 2.34 times less likely to require rescue medication at an earlier time point than episodes for famotidine 10 mg FCT, antacid 21 mEq and placebo patients, respectively ($p=<0.001$ for all).

5. EFFICACY RESULTS – PROTOCOL 110

Protocol 110 was essentially of the same clinical design as protocol 127. In the prior submission for this FACT (famotidine antacid combination chewable tablet) product, only Study 110 demonstrated that the combination therapy was statistically superior to famotidine for onset of relief of heartburn symptoms and provided longer lasting duration of relief of heartburn symptoms compared to the antacid component alone. In the agency's (FDA) non-approval letter dated February 19, 1999, it was clearly stated that approval of this application was contingent upon confirmation of the results of Study 110 by another study.

Statistical review of Study 110 revealed confirmation of statistically significant efficacy of FACT i.e., FACT demonstrated a faster onset of symptom relief than famotidine alone and a longer duration of effect than antacid alone when the sponsor's generalized estimating equations (GEE) analysis for time ordered categorical data was utilized. These analyses were based on patient-episodes. The statistical reviewer came to the conclusion that the results of the analyses were method dependent. He found that utilizing Fisher's exact analysis demonstrated lack of significant advantage of FACT over placebo for both onset and duration, over famotidine for onset, and over antacid alone for duration.

The medical reviewer had a few concerns about the study. He noted that the end points were entirely subjective and not easy to quantitate or interpret, there were statistical concerns about the GEE method of analysis, and the incremental clinical benefit of the FACT product over famotidine or antacid was only marginal. However, analysis of Protocol 110 by the GEE method did provide sufficient convincing evidence for statistically significant benefit of FACT to recommend approval pending duplication of these results.

Table 13 summarizes the comparison of treatments in Protocol 110, therapeutic gains and the statistical significance of these comparisons.

Table 13
Protocol # 110
Comparison of Treatments
Therapeutic Gain of FACT (Famotidine/Antacid Combination) over Comparators
All Percentages Statistically Significant (p=0.050) Except Where Noted (N. S.)

	FACT vs FAMOTIDINE 10-mg FCT Percentage Therapeutic Gain	FACT vs ANTACID 21 mEq Percentage Therapeutic Gain	FACT vs PLACEBO Percentage Therapeutic Gain
Onset of Action	Primary Comparator		
15 Min	6.7	1.9	11.3
30 Min	7.5	4.4	12.3
45 Min	6.0	7.2	10.2
60 Min	4.9	8.3	7.6
120 Min	3.8	6.5	7.8
Duration of Action		Primary Comparator	
≥ 7 Hrs	2.1 N. S.	9.1	11.4
6 Hrs	2.2 N. S.	9.6	11.2
5 Hrs	2.1 N. S.	9.4	10.0
4 Hrs	1.8 N. S.	6.0	8.3
< 4 Hrs	2.8 N. S.	5.8	5.8
Global Evaluation			
Excellent	5.6 N. S.	11.5	15.1
Good	0.2 N. S.	8.9	11.6
Time to Rescue Medication			
≤ 4 Hours	-3.5	-7.1	-6.9
≤ 6 Hours	-4.9	-8.4	-10.7
≤ 8 Hours	-3.5	-7.3	-11.0
Successful Treatment †			
15 Min	5.6	5.2	11.6
30 Min	5.7	9.0	13.6
45 Min	5.3 N. S.	11.1	14.1
60 Min	4.4 N. S.	11.3	12.8

† Defined as adequate relief sustained through 8 hours post-dose and requiring no rescue medication

This table demonstrates the therapeutic gains of [FACT] the famotidine/antacid combination in onset of action from 15 to 120 minutes by 3.8 to 7.5% and 7.5% at 30 minutes over famotidine. It also demonstrates the therapeutic gains of [FACT] the famotidine/antacid combination in duration of action from <4 to ≥7 hours by 5.8 to 9.6% and 9.6% at 6 hours over antacid. All these therapeutic gains (based on analysis by GEE methodology) are statistically significant.

Table 14 summarizes the comparison of treatments in Protocol 127, therapeutic gains and the statistical significance of these comparisons in a similar format to that for Protocol 110.

Table 14
Protocol # 127
Comparison of Treatments
Therapeutic Gain of FACT (Famotidine/Antacid Combination) over Comparators
All Percentages Statistically Significant (p=0.050) Except Where Noted (N. S.)

	FACT vs FAMOTIDINE 10-mg FCT Percentage Therapeutic Gain	FACT vs ANTACID 21 mEq Percentage Therapeutic Gain	FACT vs PLACEBO Percentage Therapeutic Gain
Onset of Action	Primary Comparator		
15 Min	6.0	1.3 N. S.	8.3
30 Min	6.0	3.6 N. S.	9.7
45 Min	6.7	3.6 N. S.	8.8
60 Min	7.9	3.5 N. S.	8.5
120 Min	6.9	2.8 N. S.	8.3
Duration of Action		Primary Comparator	
≥ 7 Hrs	10.0	11.5	18.6
6 Hrs	9.2	10.6	18.1
5 Hrs	9.4	7.9	17.6
4 Hrs	6.1	8.1	14.9
< 4 Hrs	6.1	6.1	7.2
Global Evaluation			
Excellent	8.2	9.4	13.5
Good	8.5	9.0	16.1
Time to Rescue Medication			
≤ 4 Hours	-7.8	-8.6	-13.2
≤ 6 Hours	-8.9	-10.6	-18.3
≤ 8 Hours	-10.5	-12.7	-19.5
Successful Treatment †			
15 Min	8.3	7.3	12.4
30 Min	8.8	10.9	15.2
45 Min	10.4	10.4	16.2
60 Min	11.2	13.2	18.6

† Defined as adequate relief sustained through 8 hours post-dose and requiring no rescue medication

Table 14 demonstrates the therapeutic gains of [FACT] in the primary parameters (onset of action and duration of adequate symptom relief), the secondary parameter (global evaluation), and exploratory parameters (time to rescue medication and successful treatment). The famotidine/antacid combination demonstrated therapeutic gains in onset of action at 15 to 120 minutes by 6.0 to 7.9% and 6.0% at 30 minutes over famotidine. FACT [the famotidine/antacid combination] demonstrated therapeutic gains in duration of action from <4 to ≥7 hours by 6.1 to 11.5% and 10.6% at 6 hours over antacid. All these therapeutic gains (based on analysis by GEE methodology) were statistically significant.

Additionally Protocol 127 demonstrated statistically significant advantages in global evaluation (secondary parameter), and time to rescue medication and successful treatment criteria (exploratory parameters).

6. BIOAVAILABILITY STUDY MK-208C - PROTOCOL - 126

Study Rationale

This single dose open-label, two-period crossover study was designed to assess the bioequivalence of famotidine/antacid combination tablets (FACT) administered without water compared to FACT administered with water.

In healthy subjects, the plasma half-life of famotidine was 2 to 3 hours. Peak plasma concentration occurred at 1 to 3 hours and is dose related. Oral dosing with 40 mg q.d. resulted in mean peak plasma concentrations of about 130 ng/mL. No accumulation occurred on repeated dosing, and plasma concentrations fall to <1 ng/mL before subsequent dosing. The mean bioavailability of an oral dose was approximately 40%. Protein binding was relatively low (15 to 20%). Following oral doses, the mean urinary excretion of the absorbed dose was approximately 70%; renal clearance was about 250 to 450 mL/min. Less than 10% of the administered dose was metabolized to a sulfoxide

Ideally, the type and dose of antacid included in a fixed combination tablet should not reduce the absorption of famotidine. The most popular antacids contain either aluminum hydroxide (e.g., MYLANTA™ Liquid [aluminum hydroxide, magnesium hydroxide, and simethicone, Johnson & Johnson-MERCK Consumer Pharmaceuticals Co.]) or calcium carbonate (e.g., TUMS™ [calcium carbonate; SmithKline-Beecham]). In a prior study, coadministration of MYLANTA™ H (aluminum hydroxide) up to a dose of 46 mEq acid neutralizing capacity (ANC) had no significant effect on the pharmacokinetics of 10 to 20 mg of famotidine. A more recent study showed that coadministration of $CaCO_3$-$Mg(OH)_2$ 42 mEq and famotidine 10 mg resulted in a 14 to 15% decrease in AUC and C_{max} when treatments were administered in the

fasted state. Although there was no available data on the effect of 21 mEq of calcium carbonate on the absorption of famotidine, those results are not clinically relevant.

Merck Research Laboratories conducted factorial efficacy studies of a famotidine/antacid combination tablet that contained 10 mg of famotidine and antacid with 21 mEq ANC. In those studies, the chewable combination tablet was administered with 60 mL of water. It would he more convenient for patients if the tablet could be taken without water being required. Water is not required for antacids to be effective. If the bioavailability of famotidine is not significantly decreased when the combination tablet is taken without water, then it would be reasonable to conclude that the benefits of the combination tablet versus its components should be maintained even when the tablet is taken without water.

Study Results

This study assessed whether a chewable fixed combination of famotidine 10 mg and antacid (calcium carbonate-magnesium hydroxide, 21 mEq ANC) administered without water is bioequivalent, with respect to famotidine, to the same administered with 60 mL of water.

Protocol 126 demonstrated that 60 mL of water did not influence the rate and extent of famotidine absorption when administered as FACT. The data showed that FACT administered without water is bioequivalent (with regard to famotidine) to FACT administered with 60 mL of water. (See Biopharm Review for results of the bioequivalence clinical study report for Protocol 126).

Given that 60 mL of water did not increase the absorption of famotidine from FACT. and that antacids, in a variety of forms, are commonly taken and known to be effective without water, the FACT label should not include a direction that the product needs to be taken with water. This will provide a benefit to the consumer by allowing more convenient dosing when water is not easily accessible

7. INTEGRATED SUMMARY OF EFFICACY

Merck Research Laboratories (MRL) completed Protocol 127 which replicated the results of 110. Protocol 127 was virtually identical to Protocol 110. Both consisted of 4 arms: FACT, famotidine, antacid and placebo. The primary difference between the 2 trials was the larger sample size in Protocol 127 compared to Protocol 110 (approximately 400 versus 300 patients/group). The results demonstrated that the famotidine/antacid combination tablet (FACT) had a clinically and statistically faster onset of heartburn relief than famotidine 10 mg. and a clinically and statistically longer duration of heartburn relief than the antacid component. The combination and both components were also statistically superior to placebo. Preplanned analyses showed that the onset and duration benefits of the combination were demonstrable within the same patient when the analysis was performed utilizing GEE method.

Table 15, supplied by the sponsor, summarizes the statistical comparisons of interest from Protocols 127 and 110. The format of the table was based on the FDA's table included in Item A of the Not Approvable Letter. This table shows that Protocol 127 confirms the results of Protocol 110 and should be considered the second adequate and well controlled trial that demonstrates the superiority of the combination relative to each of the individual components.

Table 15
Primary Analysis Results (p-values) Across the Two Studies
(Generalized Estimating Equations for Ordered Categorical Data)

		Study Protocol #	
		110	**127**
Onset of Adequate Relief	FACT vs. placebo	<0.001	<0.001
	FACT vs. famotidine	0.011	0.001
	Antacid vs. placebo	0.050	0.003
Duration Of Adequate Relief	FACT vs. placebo	<0.001	<0.001
	FACT vs. antacid	0.001	<0.001
	Famotidine vs.placebo	0.001	0.001

Table and p-values supplied by sponsor

Additional comparator tables prepared by the medical reviewer confirm the therapeutic gains achieved by FACT over the comparators in both of these clinical trials. Table 16 demonstrates the therapeutic gains achieved in both studies for the primary parameters the sponsor proposes to use in the OTC labeling i.e., onset of adequate relief at 30 minutes and duration of adequate relief $\geq$ 6 hours.

Table 16
Primary Analysis Results (p-values) Across the Two Studies
At Predetermined Time Points
(Generalized Estimating Equations for Ordered Categorical Data)
All Percentages Statistically Significant ($p \leq 0.050$) Except Where Noted (n.s.)

		Therapeutic Gain %	
	Comparisons	**Study Protocol #**	
		P 110	**P127**
Onset of Adequate Relief At 30 Minutes	FACT vs. Famotidine	7.5	6
	FACT vs. antacid	4.4	3.6 n.s.
	FACT vs. placebo	12.3	9.7
Duration of Adequate Relief $\geq$ 6 Hours	FACT vs. Famotidine	2.2 n.s.	9.2
	FACT vs. antacid	9.6	10.6
	FACT vs. placebo	11.2	18.1.

Table 17 displays the therapeutic gains achieved in both studies for the secondary (global evaluation) and exploratory parameters (time to rescue medication and successful treatment) the sponsor evaluated in both protocols.

Table 17
Secondary and Exploratory Analyses Results Across the Two Studies
(Generalized Estimating Equations for Ordered Categorical Data)
All Percentages Statistically Significant ($p \leq 0.050$) Except Where Noted (N.S.)

		Therapeutic Gain %	
	Comparisons	Study Protocol #	
		P 110	P127
Global Evaluation (Excellent)	FACT vs. Famotidine	5.6 N. S.	8.2
	FACT vs. antacid	11.5	9.4
	FACT vs. placebo	15.1	13.5
Time to Rescue Medication (≤ 8 Hours)	FACT vs. Famotidine	-3.5 N.S.	-10.5
	FACT vs. antacid	-7.3	-12.7
	FACT vs. placebo	-11.0	-19.5
Successful Treatment † (30 Min)	FACT vs. Famotidine	5.7	8.8
	FACT vs. antacid	9.0	10.9
	FACT vs. placebo	13.6	15.2

† Defined as adequate relief sustained through 8 hours post-dose and requiring no rescue medication

Protocol 126 demonstrated that 60 mL of water did not influence the rate and extent of famotidine absorption when administered as FACT. The data showed that FACT administered without water is bioequivalent (with regard to famotidine) to FACT administered with 60 mL of water.

8. INTEGRATED SUMMARY OF SAFETY

The safety of famotidine/antacid combination was characterized by evaluating the incidence of clinical adverse experiences. There were no laboratory tests conducted for the evaluation of safety and this is acceptable because the amount of famotidine being tested (10 mg) is lower than that already approved for prescription indications (40 mg or higher) and found to be safe.

As the safety of both components of this combination therapy has been well studied, famotidine as a prescription drug and then as an OTC and antacid containing $CaCO_3$ and $Mg(OH)_2$ in amounts of 800 mg and 165 mg per tablet, respectively, are well known to this agency, it was not expected that safety would be an important issue in this review. Further, only fairly well subjects with heartburn were studied.

A summary of the number of clinical adverse experiences reported during the double-blind phase of the study, drug related and serious adverse experiences causing withdrawal from the double-blind phase of the study is presented in Table 18 (sponsor's Table 18).

Table 18
Protocol 127
Clinical Adverse Experience Summary
Double-Blind Phase – Safety Population (N=1640)

	FACT		Famotidine 10-mg FCT		Antacid 21 mEq		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)
Number of patients evaluated	410		411		414		405	
Number (%) of patients:								
with one or more adverse experiences†	26	(6.3)	19	(4.6)	34	(8.2)	33	(8.1)
with no adverse experience	384	(93.7)	392	(95.4)	380	(91.8)	372	(91.9)
with drug-related adverse experiences‡§	8	(2.0)	6	(1.5)	18	(4.3)	14	(3.5)
with serious adverse experiences	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
with serious drug-related adverse experiences	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an adverse experience	0	(0.0)	0	(0.0)	3	(0.7)	4	(1.0)

† Statistically greater incidence in the antacid 21 mEq group (p=0.046) and the placebo group (p=0.045) versus famotidine 10-mg FCT.
‡ Statistically greater incidence in the antacid 21 mEq group versus famotidine 10-mg FCT (p=0.021).
§ Adverse experiences considered by the investigator to be possibly, probably, or definitely related to study drug.

A greater proportion of patients in the antacid 21 mg. (8.2%) and placebo (8.1%) groups experienced one or more adverse experiences than patients in the famotidine 10 mg FCT group (4.6%) (p=0.046 and p--0.045, respectively). A greater proportion of patients in the antacid 21 mEq group (4.3%) experienced a drug-related adverse experience than patients in the famotidine 10-mg FCT group (1.5%) (p=0.021).

The most frequently reported adverse experiences were headache and diarrhea. A greater proportion of patients in the antacid 21-mEq group experienced a digestive system disorder than patients in the FACT and famotidine groups. A greater proportion of patients in the placebo

group (2.2%) experienced a nervous system and psychiatric disorder than patients in the famotidine 10-mg group (0.5%) (p=0.036).

Considering that a total of 1640 individual participants participated in Protocol 127 in approximately 6400 total exposures to trial therapy, the total number of adverse events was extremely low. Table 19 (adapted from sponsor's table 19) summarizes the incidence and demonstrates that exposure to FACT did not significantly increase the likelihood for adverse events.

Table 19
Study 127
Number (%) of Patients with Clinical Adverse Experience
Double-Blind Phase – Safety Population (N=1640)

	FACT			Famotidine 10			Antacid 21 mEq			Placebo		
	n	%	DR	n	%	DR	n	%	DR	n	%	DR
Total Patients	410			411			414			405		
≥ 1 AE	26	6.3	8	19	4.6	6	34	8.2	18	33	8.1	14
No AE	384	93.7		392	95.4		380	91.8		372	91.9	
Body as a whole	5	1.2	2	3	0.7	1	6	1.4	4	3	0.7	1
Digestive system	8	2.0	5	6	1.5	4	19	4.6	15	12	3.0	10
MuscSkel system	1	0.2	0	2	0.5	0	2	0.5	1	3	0.7	0
NervPsych syst	6	1.5	1	2	0.5	1	9	2.2	2	9	2.2	3
Resp system	4	1.0	0	4	1.0	1	3	0.7	0	4	1.0	0
SkinAppendages	1	0.2	0	1	0.2	0	1	0.2	0	2	0.5	0
Special senses	1	0.2	0	2	0.5	0	0	0.0	0	0	0.0	0
Urogenital sys	1	0.2	0	2	0.5	0	1	0.2	1	1	0.2	0

DR = Drug related
Although a patient may have had two or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.

Those patients who had serious clinical adverse experiences during the study, were definitely not related to study drug.

2 page(s) of revised draft labeling has been redacted from this portion of the review.

10. SELECTION OF NAME

Labeling considerations are pending a consult for the selection of an approvable name by OPDRA.

11. SUMMARY OF BENEFITS, RISKS OF PROPOSED FORMULATION

Study 127 is a convincing confirmatory study utilizing similar design to study 110. The combined results of study 110 and 127, based on a similar design, reproduced similarly convincing data. The new FACT product appeared to have fulfilled its aims as being an acceptable, easily chewable tablet with prompt efficacy in providing adequate relief of meal-induced heartburn, significantly faster than provided by famotidine 10 mg and at least as rapidly as antacid tablets containing 800 mg of $CaCO_3$ and 165 mg of $Mg(OH)_2$ with 21 mEq of ANC. At the same time, and in the same participants, it appeared to have sustained adequate relief for at least 7 hours that is significantly superior to the antacid and placebo and at least as good as famotidine alone. These features are what the sponsor set out to prove, in formulating the FACT product and testing it for bioequivalence in a small clinical trial.

There were no clinically significant risks of the FACT product used as directed in the proposed OTC labeling.

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ON ORIGINAL

12. REGULATORY RECOMMENDATIONS

Study 127, the confirmatory study recommended by the agency (FDA), like Study 110 showed convincingly that the new FACT product is significantly more rapid in providing relief of heartburn symptoms than did famotidine 10 mg alone, and was significantly longer acting than 21 mEq of antacid alone. The protocol prospectively specified analyses showed that the famotidine/antacid combination tablet (FACT) had a clinically and statistically faster onset of heartburn relief than famotidine l0 mg, and a clinically and statistically longer duration of heartburn relief than the antacid alone component. The combination and both components were also statistically superior to placebo.

This medical reviewer now finds the evidence of clinical effectiveness and safety sufficiently persuasive to justify approval. While the incremental clinical benefit of the combination product is modest, it does meet the necessary statistical standards required for approval.

/S/

Scheldon Kress, M.D. Date

cc:
NDA 20-958
HFD-180/Division File
HFD-180/LTalarico
HFD-180/SAurecchia
HFD-180/HGallo-Torres
HFD-180/SKress
HFD-180/PLevine
HFD-180/MAdams
HFD-180/JChoudary
HFD-180/Melashoff

Appendix 1 Multiple-dose Dairy Cards Week 1 and Weeks 2 & 3

APPEARS THIS WAY
ON ORIGINAL

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Multiple-Dose Study

WEEK 1 EVALUATIONS – Diary Card #1

D1 __ of __

IND	Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
	0208C	127-00			1-3			

NOTE: The following information is to be recorded by the patient.

Record date and time test medication was taken and record baseline heartburn severity at that time.

Date ______________ (month/day/year) Time: ______:______ ☐ a.m. ☐ p.m. | 01 Mild | 02 Moderate | 03 Severe

Set Timer as instructed on your Diary Card #1 instructions

Time from study medication	Clock Time	Do you have adequate relief of your heartburn symptoms at this time?
15 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
30 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
45 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
1 hour	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐

Record date and time test medication was taken and record baseline heartburn severity at that time.

Date ______________ (month/day/year) Time: ______:______ ☐ a.m. ☐ p.m. | 01 Mild | 02 Moderate | 03 Severe

Set Timer as instructed on your Diary Card #1 instructions

Time from study medication	Clock Time	Do you have adequate relief of your heartburn symptoms at this time?
15 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
30 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
45 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
1 hour	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐

Record date and time test medication was taken and record baseline heartburn severity at that time.

Date ______________ (month/day/year) Time: ______:______ ☐ a.m. ☐ p.m. | 01 Mild | 02 Moderate | 03 Severe

Set Timer as instructed on your Diary Card #1 instructions

Time from study medication	Clock Time	Do you have adequate relief of your heartburn symptoms at this time?
15 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
30 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
45 min	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
1 hour	____:____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐

I confirm that the information I have recorded on this diary card is accurate: ________ (Patient's Initials) ___/___/___ (Date (month/day/year))

Investigator's name:	Staff's initials:	Date:

Multiple-Dose Study

WEEKS 2 & 3 EVALUATIONS – Diary Card #2

D2-1

IND	Compound	Protocol	Study Site	IIN	VISIT	Patient's/Subject's ID	Baseline No.	Allocation No.
—	0208C	127-00			1-3			

NOTE: The following information is to be recorded by the patient.

LM Record date and time test medication was taken and record baseline heartburn severity at that time.

Date _____ (month/day/year) Time: _____:_____ ☐ a.m. ☐ p.m. ☐ 01 Mild ☐ 02 Moderate ☐ 03 Severe

LR ***Set Timer as instructed on your Diary Card #1 Instructions***

Time from study medication	Clock Time	Do you have adequate relief of your heartburn symptoms at this time?
15 min	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
30 min	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
45 min	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐
1 hour	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐ No ☐

Set Timer for evaluations at 1 hour intervals

2 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐
3 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐
4 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐
5 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐
6 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐
7 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐
8 hours	_____:_____ ☐ a.m. ☐ p.m.	Yes ☐	No ☐	Sleeping ☐

LE

Did you take antacid during this 8-hour period? No ☐ Yes ☐
If yes, record name and time taken below.

Antacid Name:

_____ _____ **Time:** _____:_____ ☐ a.m. ☐ p.m.

Did you eat or drink anything during this 8-hour period? No ☐ Yes ☐

If yes, what time did you eat or drink? **Time:** _____:_____ ☐ a.m. ☐ p.m.

I confirm that the information I have recorded on this diary card is accurate: _____ (Patient's initials) ___/___/___ (Date (month/day/year))

Investigator's name:	Staff's initials:	Date:

Appendix 2

Table 1 A
Study P 127
Serious Protocol Violators (N=49)

Protocol Violation	Investigator†	Allocation Number(s)	Treatment Group
Inappropriately randomized due to inadequate relief of heartburn within 1 hour for ≥50% of episodes during run-in phase.	127-012 127-015 127-020 127-023	1133 0847 1163 1344	FAM 10 mg AA 21 mEq FAM 10 mg FAM 10 mg
Inappropriately randomized due to inability to complete study diary as specified.	127-011	0601	FACT
Inappropriately randomized because patients repeatedly took double-doses of baseline antacid during run-in phase.	127-006 127-027 127-031	0303 1590 1797	Placebo FAM 10 mg FACT
Took doses of study medication <7 hours apart at least once during treatment phase.	127-007 127-025 127-026 127-032	0406 1472 1550 1835	FACT Placebo FACT FAM 10 mg
Prohibited concomitant medication. (oxybutynin chloride) (clidinium bromide) (oxybutynin chloride) (prednisone). (lansoprazole). (amitriptyline) (imipramine HCl). (nabumetone. methotrexate) (methadone) (amitriptyline)	 127-005 127-006 127-014 127-021 127-023 127-026 127-027 127-033	 0255 0312 0804 1213 1241 1338 1349 1367‡ 1547 1557 1616 0326 0332	 FAM 10 mg Placebo AA 21 mEq Placebo FACT AA 21 mEq FACT AA 21 mEq Placebo AA 21 mEq FACT Placebo FAM 10 mg

Table 1 B
Study P 127
Serious Protocol Violators (N=49)

Protocol Violation	Investigator†	Allocation Number(s)	Treatment Group
Inconsistent dosing information on study diary.	127-004	0210	FACT
	127-010	0543	Placebo
	127-012	0676	FAM 10 mg
		1691	Placebo
	127-014	0791	Placebo
		0795	AA 21 mEq
		0796	Placebo
		0797	FACT
	127-019	1087	Placebo
	127-020	1188	Placebo
		1192	Placebo
	127-023	1321	Placebo
	127-025	1442	FAM 10 mg
	127-026	1513	AA 21 mEq
		1524	FAM 10 mg
	127-029	1412	FACT
	127-030	0124	Placebo
	127-033	0327	FACT
Took study medication and rescue medication at same time.	127-023	1367‡	AA 21 mEq
	127-028	1646	Placebo
	127-029	1407	FACT
	127-034	0765	AA 21 mEq
Missing heartburn relief evaluations for more than 50% of evaluations during treatment phase.	127-025	1441	FACT
	127-029	1382	FAM 10 mg
	127-029	1385	FACT

‡ Patient violated two exclusion criteria.

3 page(s) of revised draft labeling has been redacted from this portion of the review.

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S NEW DRUG APPLICATION (NDA) REVIEW

NDA:	20-958
SPONSOR:	Johnson & Johnson Merck Consumer Pharmaceuticals c/o Merck Research Laboratories, West Point PA 19486
DATE OF SUBMISSION:	20 February 1998
DATE OF RECEIPT:	20 February 1998
DRUG:	PEPCID® Premier TABLETS (Famotidine/Antacid Combination) for over-the-counter (OTC) consumption; famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg (21 mEq acid-neutralizing capacity).
ADMINISTRATION:	Oral, chewable, mint tablet, up to twice in 24 hours for up to 2 weeks, for persons 12 years of age and older
INDICATIONS:	Relief of heartburn, acid indigestion, and sour stomach (acid reducer and antacid).
MATERIAL REVIEWED:	Application, 25 volumes; data from four pharmacology (clinical) and five clinical studies; proposed OTC labeling; pertinent other information and references.
REVIEWER:	John R. Senior, M.D./ 21 January 1998

JAN 2 2 1999

Brief Overall Summary

The sponsor has requested approval of a new famotidine-antacid combination tablet (FACT) proposed for OTC marketing for relief of heartburn, acid indigestion, and sour stomach. The rationale for providing this combination tablet was that it would be more rapidly beneficial than famotidine alone and longer acting than antacid alone, in a single chewable tablet. At the same time, it was important that neither the rapidity of antacid effect be impaired by adding famotidine, nor the duration of famotidine effect be impaired by addition of antacid. It was also made clear that both beneficial effects would have to be demonstrable in the same persons, who were to be compared by proportions of them achieving successful benefit by all these criteria. The new FACT product was tested in full factorial design (FACT, famotidine alone, antacid alone, and neither (double placebo) in a series of four biopharmaceutical studies in 88 subjects, pilot clinical studies of 474 and 329 participants, three large clinical trials in 3645 participants, and a use study of 496 consumers. The results showed FACT only in one study (Study 110) to be significantly faster than OTC famotidine in giving adequate relief of spontaneous and test-meal-induced heartburn, significantly longer in sustained adequate relief than antacid or placebo, as well as at least as good as antacid for prompt effect and as famotidine for long effect. There was no increased safety risk. It is recommended that a confirming study be done to justify approval.

Table of Contents

I. Introduction

A. Approach to the review and conventions used

The reviewer has approached this submission by focusing first upon what the sponsor has requested, and listing what evidence has been submitted in support of that request. The title page shows the sponsor, the drug product, dates of submission and review, and materials reviewed. Immediately following is a boxed, concise, half-page summary of the review, to provide the reader with a preliminary picture of the purpose, context, issues, major findings and conclusions, evaluation and regulatory recommendations. The organization of the review and a road map to its sections in a Table of Contents follows on the second page, and that is immediately followed by this explanation of the process used to approach the information submitted in the 25 volumes (and electronic submission).

The convention used in the review, to distinguish the sponsor's data and interpretations from the reviewer's abstracting, paraphrasing, or summarization of the submitted material, and from reviewer-generated opinions and discussion, was to use typeface variants:

Material summarized by the reviewer from that submitted by the sponsor is shown in plain 12-point Times New Roman font, with references to Volume and page numbers in the submitted material;

Text taken directly from that submitted by the sponsor is shown in quotations, and tables or figures copied from the submitted material were noted "As submitted in Volume ___, page ___."

Commentary, opinion, discussion by the reviewer about the submitted material or about the literature or other sources (cited, wherever possible) was shown in 12-point italic Times New Roman font.

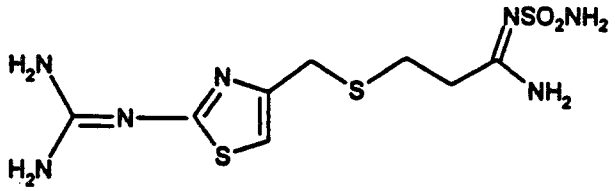
Material provided by the reviewer in explanation of the approach taken to review, or taken from other sources, whether pertinent literature or other regulatory material, shown in 11-point font;

Sections of the review were numbered and paginated as shown in the Table of Contents. These corresponded in general with the "Guideline for the Format and Content of the Clinical and Statistical Sections of an Application," published in July 1988 by the Center for Drug Evaluation and Research of the Food and Drug Administration.

In this particular review, the principal data submitted were four clinical pharmacology studies and three major clinical trials, comprising 3645 randomized participants (3616 treated), according to the sponsor's cover letter (Volume 1 of 25). The application was submitted as 25 printed volumes, with case report forms and tabulations electronically on compact disks and later (March 1998) as a complete electronic submission.

B. Description of the drug

Famotidine used in this combination OTC product is the same drug as previously approved for both prescription use and as a single OTC 10-mg tablet product. Its formal chemical name is 3-[[[2-[(Amino imino methyl) amino] -4-thiazolyl] methyl] thio]-N-(amino sulfonyl)-propanimidamide, formula $C_8H_{15}N_7O_2S_3$, molecular weight 337.43; it was originally patented in Belgium, United States, and Japan in 1980 and 1981 by Yamanouchi.



famotidine

It is a white to pale yellow crystalline compound that is soluble in dimethylformamide and acetic acid, very slightly in methanol and water, and almost insoluble in ethanol, ethyl acetate, and chloroform.

Famotidine is a competitive inhibitor of histamine type 2 receptors (H2-blocker) that acts to inhibit gastric secretion both of acid concentration and volume of gastric juice, and of pepsin in proportion to the volume reduction. Both basal and nocturnal gastric secretions are reduced, and also secretion stimulated in response to food and pentagastrin. After oral administration, onset of antisecretory effect begins within one hour, shows a dose-dependent maximum effect between one and three hours, and inhibition lasts 10 to 12 hours after doses of 20 and 40 mg.

As summarized in the approved labeling, oral doses of PEPCID (famotidine, Merck) as tablets or suspension (40 mg/5 mL) are bioequivalent, and show absolute bioavailability of 40-45%. Absorption of famotidine is slightly increased by food and slightly decreased by antacids, but the effects of the difference were not judged clinically important, as stated in the approved labeling. Famotidine is about 15-20% protein-bound in plasma, undergoes very little first-pass metabolism, and shows a plasma half-time of 2.5-3.5 hours, being eliminated mainly by urinary excretion (65-70% as intact drug) but also by metabolism (30-35%). The principal human metabolite is the S-oxide derivative. About 25-30% of an oral dose and 65-70% of an intravenous dose may be recovered unchanged in the urine. Therefore, participants with renal insufficiency and reduced creatinine clearance may need dose reduction, since elimination half-time may exceed 20 hours. No clinically significant age-related changes in famotidine pharmacokinetics have been found, nor need for dose reduction in the elderly.

Because famotidine as well as three other "H2-blockers" cimetidine, ranitidine, and nizatidine are all approved for OTC use in dosages reduced from those approved for indications such as healing peptic ulcers, it may be pertinent to compare their pharmacodynamic effects in reducing gastric acid secretion, as reported in their approved labeling. The small table immediately following summarizes the duration and extent of inhibition of nocturnal gastric acid secretion after oral dosing:

COMPARISON OF INHIBITION OF NOCTURNAL GASTRIC ACID SECRETION BY H2-BLOCKING AGENTS

agent trade name	oral dose mg	plasma half-time, hr	percent inhibition nocturnal secretion	duration of inhibition
famotidine (Pepcid®, Merck)	20 or 40	2.5 – 3.5	86 or 94	up to 10 hr
Cimetidine (Tagamet®, SmithKline	300	2.0	not stated in label basal 80%	- 4 – 5 hr
Ranitidine (Zantac®, Glaxo-Wellcome	150	2.5 – 3.0	92	up to 13 hr
Nizatidine (Axid®, Lilly)	300	1 - 2	90	up to 10 hr

The four H2-blocking agents above are all approved for OTC use, in lower doses, and it may be expected that competitive pressures will lead to other H2-blocker/antacid combination products that will be considered for evaluation in the OTC market.

Famotidine is approved for prescription use to heal duodenal ulcers and benign gastric ulcers, in doses of 40 mg daily at bedtime or 20 mg b.i.d., usually for 4 weeks for duodenal ulcers and 6 weeks for gastric ulcers, with a few participants needing treatment for the latter indication for up to 8 weeks. It is also approved for maintenance treatment to reduce recurrence of duodenal ulcers, at 20 mg at bedtime daily for up to a year. Doses of 20 or 40 mg b.i.d. are approved for up to 12 weeks for healing of erosive esophagitis associated with gastroesophageal reflux disease (GERD), and 20 mg b.i.d. for up to 6 weeks for treatment of GERD symptoms. For pathological gastric hypersecretion, such as may occur in Zollinger-Ellison syndrome , higher doses may be used, starting with 20 mg every 6 hours, but up to 160 mg every 6 hours may be needed in some participants. An intravenous formulation is also available for short-term treatment of participants unable to take oral medications , in daily doses of 20 mg every 12 hours, adjusted downward in renal insufficiency and upward in hypersecretory states.

Famotidine is also available as Pepcid AC (Acid Controller) tablets for OTC use, containing 10 mg of famotidine per tablet (prescription tablets of Pepcid contain 20 or 40 mg famotidine and are distinctly different in appearance). The OTC formulation is marketed by Johnson & Johnson – Merck Consumer Pharmaceuticals as square, rose-colored tablets marked 'PEPCID AC' for relief of heartburn and acid indigestion, and also for prevention of heartburn and acid indigestion brought on by consuming food and beverages (when taken one hour before the meal expected to cause symptoms). The instructions provide that one tablet be swallowed with water, and that no more than two tablets be taken within 24 hours, and also that the product not be given to children under 12 years of age unless directed by a doctor. Consumers are advised not to use maximum doses of two/day for more the two weeks, if pregnant or nursing, or if persistent abdominal pain or swallowing difficulty are present, without medical supervision.

The composition of the famotidine-antacid combination tablet (FACT) proposed for marketing, and used in most of the clinical pharmacology and clinical studies described below is formulation C-675-8C, ingredients of which are *(Volume 3, page 152)*:

Table D-1 Market Composition

Component	Reference	Role	mg/tablet
Sugar	NF		
Magnesium Stearate	NF		
Famotidine	USP		10.00
Lactose	NF		
Hydroxypropyl Methylcellulose	USP		
Cellulose	NF		
Hydroxypropyl Cellulose	NF		
Calcium Carbonate			
Magnesium Stearate			
Total Tablet Weight (mg)			**1780**

(1) Used in the manufacture of tablets, but removed during the manufacturing process.
(2) Contains 98% $Mg(OH)_2$ = 165 mg/tablet
(3) Contains 95% $CaCO_3$ = 800 mg/tablet, 42.1 mg/tablet pregelatinized starch NF and a trace quantity of sodium lauryl sulfate NF.
(4) Letters of Authorization found in Section I.C.2.a.

Batch Number: C-675-8C

Comment: It may be noted that — of peppermint flavoring was included in the FACT product, and — of peppermint plus — of spearmint flavoring were also in the antacid and placebo tablets made up for comparisons in these studies, but not in the marketed famotidine 10-mg tablets used (referred to as famotidine coated tablets "FCT" in these studies). While it has been claimed that such mint flavorings may have effects on the lower esophageal sphincter, the presence of almost as much mint in the antacid and placebo controls reasonably well obviates the effect of mint flavoring in the differential effects of the products, except for the FCTs.

C. Background of previous NDAs approved for famotidine

Famotidine was the third "H2-blocker" approved in the United States, after cimetidine and ranitidine. Application for the tablet preparation was approved 15 October 1986 (NDA 19-462). The intravenous 10 mg/mL and the suspension 40 mg/mL products were approved 4 November

1986 (NDA 19-510) and 2 February 1987 (NDA 19-527), respectively. A pre-mixed intravenous formulation was subsequently approved 18 February 1994 (NDA 20-249), and a rapidly disintegrating oral tablet was very recently approved on 28 May 1998 (NDA 20-752). A preparation of famotidine gelcaps was submitted for review 30 September 1997 (NDA 20-902) and review is pending.

For OTC use, famotidine as PEPCID AC (Acid Controller tablets containing 10 mg of the active drug) was approved 28 April 1995, for use up to two tablets/24 hours for no more than two weeks without medical advice. It was approved for indications as stated above, and was co-marketed with the Johnson & Johnson Company as a tablet for swallowing with water, for adults and adolescents, but not for children under 12 years of age unless directed by a doctor.

The famotidine-antacid combination product under consideration in this application was submitted as an investigational agent (IND ——) on 17 May 1996. It also was intended for co-marketing with J & J as a product faster acting than famotidine and longer acting than antacid.

D. Present labeling for famotidine OTC tablets

PEPCID AC (Acid Controller tablets containing 10 mg of famotidine) are sold OTC to consumers for both relief of heartburn and acid indigestion or sour stomach and prevention of those symptoms brought on by consuming food and beverages. Consumers are instructed to swallow 1 tablet with water for relief of symptoms, and for prevention of the symptoms to do so 1 hour before eating a meal expected to cause symptoms. They are instructed that up to 2 tablets may be taken within 24 hours, and that children under 12 years of age should not be given the tablets unless it is directed by a doctor.

Consumers are supposed to be told not to take the maximum daily dose of 2 tablets for more than 2 weeks except under the advice and supervision of a doctor. They are also supposed to be informed that they should see a doctor promptly if they have trouble swallowing or persistent abdominal pain, which could indicate a serious condition that may need different treatment. If pregnant or nursing, they are advised to seek advice of a health professional before taking PEPCID AC tablets.

It is also included in the printed labeling, not on the box but in the package insert, that there are some ways that they may help avoid symptoms:

- Do not lie down soon after eating.
- If you are overweight, lose weight.
- If you smoke, stop or cut down.
- Avoid or limit foods such as caffeine, chocolate, fatty foods, and alcohol.
- Do not eat just before bedtime.

Comment: It is not stated in the OTC labeling what problems children under 12 would be taking the tablets for, and what might be the childhood equivalent of "heartburn, acid indigestion, and sour stomach." It is also unclear for what indications the doctors may be directing use of OTC famotidine in the children and infants.

Four bar-chart graphs are provided for consumers, two each for results of clinical studies for the relief and prevention of heartburn, marked Study A, B, C, and D. The comparisons are between PEPCID AC (tablets) and placebo tablets, showing the former significantly better in relieving and preventing heartburn. It is not clear from the presentation whether numbers of participants, episodes of heartburn, severity of heartburn, or what is being compared, nor which studies are for relief and which for prevention. That, however, is past business. We shall look more closely at the new proposed information for the combination tablets.

The labeling proposed includes two bar charts (Volume 2, Section B-2, carton back panel) that compare effects of the FACT product and placebo tablets, for onset and duration of relief of heartburn symptoms. It is of little interest to prospective consumers to compare the new FACT to placebo; what they would most likely be more interested in is comparisons with antacid and FCT tablets to provide some information on whether the new FACT product has any advantages.

E. Proposed labeling for the PEPCID® ——— chewable mint tablets

Fairly similar labeling is requested for the new chewable tablets combining famotidine 10 mg (the acid reducer) and calcium plus magnesium (antacid), but consumers are to be told to chew 1 tablet of the new product thoroughly and swallow with water, for relief of symptoms of heartburn, acid indigestion, or sour stomach. Details of the changes in labeling from the PEPCID AC to the PEPCID ——— tablets are provided in pages 37-49, Volume 1, in the section on Labeling. The principal difference is that no prevention claim is being requested, since appropriate studies were not done.

Comment: Prevention of symptoms is mentioned only on the left front panel of the 30 Tablet Dispenser (pages 17 and 62, Volume 1). However, in the detailed description of changes to the labeling from the AC to the ——— tablets it is stated that the indication and instructions for prevention should have been deleted because clinical studies to support this indication for Pepcid ——— have not been conducted. This needs to be corrected to avoid possible confusion.

The new proposed labeling for the combination ——— tablets does add several new tips for managing heartburn that were not provided for the AC tablets, and rephrases some that were given before. The *new* tips to consumers are:

- Do not lie flat *or bend over* soon after eating.
- Do not eat *late at night, or* just before bedtime.
- Avoid foods or drinks that are more likely to cause heartburn, such *as rich, spicy,* fatty *and fried* foods, chocolate, caffeine, and alcohol, *and even some fruits and vegetables.*
- *Eat slowly and do not eat big meals.*
- If you are overweight, lose weight.
- If you smoke, quit smoking.
- *Raise the head of your bed.*
- *Wear loose fitting clothing around your stomach.*

New bar chart data are proposed in two sets of graphs, instead of the four provided for the AC tablets (eliminating the prevention studies). The new graphs show onset of relief of heartburn within 30 minutes in 45% of episodes after PEPCID —— tablets and 33% after taking placebo tablets, and heartburn episodes relieved for at least 7 hours as 70% after PEPCID —— tablets and 59% after taking placebo tablets.

A new precaution for consumers, under Safety Information, is that "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician or other health professional."

Comment: If studies were not done with the new famotidine-antacid combination tablets to prove prevention of heartburn or other symptoms, then it is appropriate not to make the claim in the labeling, and to change it in the new requested labeling. This has been done in most but not all places (see comment above). The addition of new tips for avoiding heartburn without medications is consistent with standard advice, and is quite acceptable. The precaution about not taking antacids with certain prescription medications is also acceptable. Whether or not consumers can understand and make decisions based on the graphic data is questionable.

F. Marketing of famotidine, prescription and OTC

The sponsor provides a statement (page D-1, Volume 2) that this combination famotidine-antacid product, PEPCID —— TABLETS, has not been approved or registered anywhere, nor as of 30 January 1998 was any application made, withdrawn, or rejected anywhere. This application represents the initial request for consideration of famotidine/antacid combination that contains famotidine 10 mg, calcium carbonate 800 mg, and magnesium hydroxide 165 mg (21 mEq acid-neutralizing capacity).

It is also stated that famotidine "has received worldwide marketing approvals for use in both prescription and nonprescription indications and formulations" but no data are provided on how much use there has been. (*See also above section C on the FDA regulatory history of famotidine.*)

The approved labeling for the OTC PEPCID AC (Acid Controller) tablets states that the [active] ingredient in the tablets, famotidine, "has been prescribed by doctors for years to treat millions of people safely and effectively." Similar language is proposed for the PEPCID —— TABLETS,

namely "The ingredients in Pepcid —— have been used for years to treat acid-related problems in millions of people."

Comment: It is true that famotidine has been very widely used, and has a good record for both safety and effectiveness for the prescribed indications for which it has been approved. It perhaps should be mentioned that peppermint and spearmint have also been included in many preparations of antacids for decades.

It is also true that the calcium carbonate and magnesium hydroxide, in the amounts contained, are quite acceptable as a safe and effective antacid under the criteria outlined in 21 CFR Ch I (4-1-98 Edition), Part 331: Antacid Products for Over-the-Counter (OTC) Human Use. The monograph requires that the finished product contain at least 5 mEq of acid neutralizing capacity (ANC), as measured by procedures of the United States Pharmacopeia 23/National Formulary 18. It also requires that each ingredient, from the list in 331.11 (includes calcium carbonate and magnesium hydroxide), contribute at least 25% to the total ANC.

In the amounts listed for the antacid content of the product, 800 mg of calcium carbonate provides 2 x 800/100.09 = 15.99 mEq and 165 mg of magnesium hydroxide provides 2 x 165/58.32 = 5.66 mEq. The total 21.65 mEq is then 74% from $CaCO_3$ and 26% from $Mg(OH)_2$, fulfilling the monograph requirements. Further, neither agent is present in excess, even if two tablets are taken within 24 hours: maximum for calcium carbonate, 160 mEq or 8 g/day; less than 50 mEq (2.9 g) of magnesium hydroxide, so no warning label for people with kidney disease is required.

Finally, the required precaution about drug interactions , section 331.30(d), is included in the new proposed labeling: "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician or other health professional."

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II. Clinical Pharmacology, Bioequivalence, Bioavailability

A. Clinical pharmacology of famotidine

The sponsor has submitted four studies of the clinical pharmacology of the combination of famotidine and antacid, two of which were single-dose, two-period crossover studies for bioequivalence to famotidine alone in the fed (Study 095) and fasting states (Study 101). Another (Study 096) was of absolute bioavailability of the combination famotidine-antacid versus intravenous famotidine 10 mg. Also investigated (Study 098) was the pharmacodynamic effect on esophageal and gastric pH of the combination product, compared to separate administration of antacid, famotidine, and neither, in single-dose, four-period crossover design. Three of the four clinical pharmacology studies were carried out in 61 healthy subjects: 24 in each of Studies 095 and 101, 13 in Study 096. For Study 098, 27 participants with heartburn history were studied. *(Please see also the review of Dr. A. R. Sancho, reviewer for Clinical Pharmacology and Biopharmaceutics.)*

Since famotidine has been extensively studied prior to approval of the several formulations that are for prescription use, and for the 10-mg tablet approved as PEPCID AC (Acid Controller) product, there is considerable background information, most of which has not been resubmitted.

In the summary background information about famotidine pharmacokinetics (Volume 6, pages 2-8), the sponsor summarizes the background information on famotidine pharmacokinetics as follows:

- famotidine pharmacokinetics (PKs) are linear over the oral dose range from 5 to 40 mg, and 38% of a radioactive dose is recovered in urine, 51% in feces;

- after intravenous administration, 71% of the famotidine is recovered unchanged in the urine, but only 28% may be so recovered after an oral dose;

- the plasma half-time averages 2.8 hours in healthy young subjects after either oral or intravenous dosing, rising to about 4 hours in healthy elderly participants, and may be up to 20 hours in peoples with severe renal functional (anuric) impairment;

- absolute bioavailability of 20-mg oral tablets averages 45%, and for 40-mg tablets, 42%. The bioavailability is slightly increased in the presence of food, and slightly decreased with antacids, but the effects are small and probably not clinically meaningful;

- bioavailability of famotidine from tablets is similar for healthy young and elderly people, and the PEPCID tablets are bioequivalent to other famotidine preparations used in studies carried out in Japan;

- famotidine exists in two polymorphic forms, Form I being thermodynamically less stable and changing slowly into Form II during tablet processing, so the finished product is comprised of a mixture. However, the solubility, melting points, and dissolution profiles are similar and the two forms are pharmacokinetically bioequivalent when administered in capsule formulations