Analyses by the per-protocol approach for 1126 participants led to the same conclusion, as did analysis of proportions of participants reporting adequate relief at 30 or 60 minutes. For the somewhat less stringent endpoint of time to at least one grade reduction in heartburn severity, the proportions of participants reporting that reduction at 30 and 60 minutes, significant differences were also seen for comparison of FACT vs placebo, as well as for FACT vs FCT. In all comparisons, FACT and antacid were not significantly different in their prompt effects on heartburn relief.

Comment: These results were as expected, based on the accumulating experience with the new FACT preparation, compared to approved FCT and antacid preparations. In all of these studies the FACT preparation used was the same C-675-8C formulation that is intended for marketing. The comparison preparations in this study were also the same as in the other studies submitted.

With respect to the *duration* of effect, the primary outcome measure had been established in the protocol as depending on proportions of participants wakened with heartburn. Based on results from Study 078, it had been estimated *(Volume 14, page 2643)* that the proportion of participants who had taken FACT for their heartburn would be significantly smaller than for those who took antacid, 58% vs 71%, and the difference of 13% would have 89% power to be significant at a two-tailed $\alpha = 0.050$, with 275 participants in each study arm. As it turned out, the proportions who were awakened by heartburn in both groups were less than seen in Study 078, and the difference was only 8% rather than 13%.

All-Patients-Treated Approach
Proportion of Patients Reporting No Awakenings With Heartburn (N=1137)

	FACT (n=282)		Famotidine 10-mg FCT (n=285)		Antacid 21 mEq (n=284)		Placebo (n=286)	
	n	(%)	n	(%)	n	(%)	n	(%)
No awakenings	158	(56.0)	141	(49.5)	137	(48.2)	123	(43.0)
Any awakenings	124	(44.0)	144	(50.5)	147	(51.8)	163	(57.0)

Data Source: [4.9]

Treatment Comparison	Model-Adjusted Odds-Ratio (95% CI)	Chi-Square	p-Value
FACT vs. FAM 10-mg FCT	1.31 (0.93, 1.83)	2.38	0.123
FACT vs. AA 21 mEq [P]	1.38 (0.98, 1.93)	3.42	0.065
FACT vs. placebo	1.72 (1.23, 2.42)	9.83	0.002
FAM 10-mg FCT vs. placebo	1.32 (0.94, 1.85)	2.58	0.108
AA 21 mEq vs. placebo	1.25 (0.89, 1.75)	1.69	0.194
FAM 10-mg FCT vs. AA 21 mEq	1.05 (0.75, 1.48)	0.10	0.758

FACT = Famotidine/antacid combination; FAM = Famotidine; AA = Antacid.
[P]: FACT vs. AA 21 mEq is the primary treatment comparison.

The participants who had taken FACT awakened with heartburn in only 44% of the cases, rather than the predicted 58%, but those who had taken antacid were awakened with heartburn only in 52% of the cases, much less than the predicted 71%. As a result, the difference between FACT and antacid was less marked, and did not reach the criterion of statistical significance set for it,

and p was only 0.065, not significant. It was noted that FACT was significantly better than placebo, however, and not significantly different than FCT. When the slightly smaller number of 1124 participants in the per protocol were evaluated, the p-value for FACT vs antacid became 0.045, and for FACT vs placebo was 0.002, both statistically significant.

For participants needing rescue antacids during the night, FACT again proved to be significantly better than placebo ($p = 0.011$) but again not significant ($p = 0.058$) for FACT vs antacid, even when the per protocol approach was used ($p = 0.059$). The overall global assessment done the next morning yielded the same results, i.e., that FACT was significantly better than placebo in producing an overnight effect, but FACT did not significantly surpass antacid. Analyses of both prompt and long effects again indicated that FACT was better than placebo but not significantly better than antacid.

Again, there were no clinically important safety problems with any of the preparations administered in this study.

In discussing the results of Study 109 *(Volume 13, pages 2477-9)*, the sponsor speculated that perhaps this study showed less nocturnal awakening than was seen in Study 078 because of the differences in which the way the studies were done. Especially noted was the lack of a bedtime snack in this study that may have reduced nocturnal awakening and heartburn symptoms to the point where expected differences between treatments were obscured. The design of this study, with no bedtime snack, a relatively great focus on prompt observations within the 2 hours after dosing, and the relative paucity of nocturnal measurements were cited as possible reasons for the failure of FACT or FCT to be significantly better than antacid in preventing awakening with heartburn symptoms. Famotidine (FCT), and especially FACT, were slightly better than antacid or placebo, but the differences were not significant except for FACT vs placebo.

Comment: The differences between treatments predicted from the pilot Study 078 that was designed and intended to simulate what participants might really do did not extend to this more exact study in which all the participants received the same meal. The new FACT preparation was clearer more rapid in its effect than famotidine alone, but for these participants the advantage of FACT or FCT over simple antacid in preventing nocturnal awakening with heartburn was small.

3. Study 110: multiple (4)-episode, at-home onset & duration of relief

Study 110 was the last of the three large clinical studies of the efficacy of the new FACT preparation (formulation C-675-8C) compared to the marketed famotidine 10-mg OTC tablet (FCT) and an antacid containing 21 mEq of ANC as $CaCO_3$ and $Mg(OH)_2$ (antacid), and to placebo was carried out from May to August 1997. A group of 15 investigators recruited a total of 2144 participants, of whom 904 were not randomized (42%) and 1240 were randomized to one of the four treatments, as previously defined and studied. The same study formulations were used as in Studies 078, 104, 106 and 109. The study focussed on spontaneous heartburn arising anytime during the day, rather than that provoked by a specific test meal, and was aimed at considering four such episodes within a period of two weeks.

Participants recruited into this study, as in the previous studies summarized above, were to be adults over 18 with histories of specifically recognized food/beverage-induced heartburn at least three times weekly for at least two months, for which they took antacids for relief. A single-blind antacid-run-in period of one week was required for demonstration of eligibility. This was based on need for antacid tablets (24 mEq ANC each) on at least 3 of the 7 days, AND either two episodes of heartburn on the day they took antacids OR need to take two doses within 8 hours, AND adequate relief of heartburn within 60 minutes of dosing for at least half of their episodes of heartburn, AND satisfactory completion of the diary card. Participants who did not meet all of those criteria were not eligible for randomization. It was initially planned in April 1997 that 1600 participants would have to be recruited and screened by 12 investigators in order to obtain 1200 who qualified for randomization and analysis *(Volume 15, pages 3144-74)*.

When evaluated as eligible by the above criteria, participants were given four blister cards of study medication (a chewable tablet and a tablet to swallow in each), a diary card, and a supply of "rescue" MYLANTA® Double Strength pink, cherry-flavored antacid tablets. They were instructed to take study medication if they developed heartburn of any intensity they felt sufficient for treatment. They were to chew one tablet, and to swallow the other with 60 mL of water [might be 1) a FACT and placebo FCT, 2) a placebo antacid and FCT, 3) an antacid and placebo FCT, or 4) placebo antacid and placebo FCT]. They were to record the time of the last meal before the episode, the intensity of the heartburn (mild, moderate, or severe), time of taking the study tablets. Thereafter they were to reassess their heartburn every 15 minutes for an hour, then hourly for another 7 hours, recording at each time whether relief was adequate or not (or sleeping). They were told not to use rescue antacid within an hour of study medication, and not to repeat study medication for at least 8 hours. They were not to eat, drink, lie down, or sleep for the first hour post-dose, then to record any food or drink taken from 1 to 8 hours post-dose. Rescue medication (one MYLANTA® Double Strength tablet) needed was to be recorded as to when taken. Participants were encouraged to use all four sets of study tablets during the two weeks of the double-blind study. Because of the complexity of this study, it may be helpful to the reader to see a copy of the Diary Card #2 on which participants recorded their double-blind *data (from Volume 15, page 3279)*:

Multiple-Dose Study

WEEKS 2 & 3 EVALUATIONS – DIARY CARD #2

D2-1

SID	Compound	Protocol	Study Site	PN		Patient's/Subject's ID	Baseline No.	Allocation No.
	208C	110-00	110-004	08622				

LM

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

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

Date: _____ (mo/day/yr) Time: : ☐ a.m. ☐ p.m. ☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe

Record the time you last ate : : ☐ a.m. ☐ p.m.

Record the time you last drank something other than water : : ☐ a.m. ☐ p.m.

Set Timer for evaluations at 15 minute intervals

LR

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 (mo/day/yr)

10 Investigator's name: William Hiegen, M.D. Staff's initials: Date:

The protocol was amended in July 1997, during the study execution, with the intent to enroll approximately 1900 participants at up to 16 study centers, to obtain post-treatment data on 1200 participants *(Volume 15, pages 3203-7)*. As stated above, 15 investigators recruited 2144 participants, found 904 not eligible for randomization, and randomized 1240 participants to study medication. The investigators and locations were: A.S. Arora, Fresno CA; W.M. Gooch, Salt Lake City UT; D. Hallbert, Rockland ME; W.J. Hisgen, Madison WI; N.M. Kassman, Statesville NC; A. Korkis, Paramus NJ; T. Marbury, Orlando FL; J.E. Pappas, Lexington KY; N. de Sola Pool, Hackensack NJ; E. Richards, Port Chester NY; R.R. Stoltz, Evansville IN; C.T. Tweel, Kettering OH; M. Posner, Huntingdon Station NY; M.D. Sarlin, Spartanburg SC; and W. Satterlee, Indianapolis IN *(Volume 15, pages 3281-2)*.

Investigator	*screened*	*ineligible*	*randomized*	FACT	FCT	antacid	placebo
Arora	257	97	160	40	40	40	40
Gooch	111	36	75	18	19	19	19
Hallbert	84	30	54	13	14	14	13
Hisgen	47	11	36	9	9	9	9
Kassman	54	25	29	7	8	7	7
Korkis	300	143	157	39	40	39	39
Marbury	44	23	21	5	5	6	5
Pappas	96	26	70	17	18	17	18
De Sola Pool	181	76	105	26	27	26	26
Richards	259	124	135	33	34	34	34
Stoltz	271	114	157	40	39	39	39
Tweel	33	8	25	7	6	6	6
Posner	100	44	56	14	14	14	14
Sarlin	118	38	80	20	20	20	20
Satterlee	189	109	80	20	20	20	20
total	2144	904	1240	308	313	310	309

The 1240 participants randomized to treatment included 6 who were known to have not taken study medication and 2 who were lost to follow-up. The "safety" population sample was taken as 1234 participants, and the "all-participants-treated" as 1232. Of the 1232 who took study medication 31 did not follow the protocol for one reason or another because their own conduct or investigator error *(Volume 15, page 3401)*, leaving 1201 studied "per protocol." Of the 1240 randomized to treatment, 829 (66.9%) were women, 1061 Caucasian (85.6%), 102 Black (8.2%), 66 Hispanic (5.3%), 11 other (0.9%). They ranged in age from 17 to 79, median 42. There were no significant differences in age, gender, race, heartburn frequency between study groups, nor among those not randomized for this study *(pages 3406-7, Volume 15)*.

The principal measures of efficacy were time to adequate relief for ***onset*** of effect within 2 hours, and for ***duration*** of effect the number of episodes of heartburn adequately relieved for at least 7 hours. The efficacy analyses were based on 4864 episodes of heartburn in 1232 treated participants. The great majority of these heartburn episodes (92%) occurred between 7 a.m. and 11 p.m., with peaks between 6-7 p.m. and 1-2 p.m. after regular evening and midday meals.

NUMBER AND (CUMULATIVE %) EPISODES ADEQUATELY RELIEVED IN 1231 PARTICIPANTS TREATED

	FACT	FCT	antacid	Placebo
adequate relief	n = 305	n = 311	n = 308	n = 307
at (minutes)	*1205 episodes*	*1229 episodes*	*1212 episodes*	*1217 episodes*
15	322 (27.0%)	249 (20.3%)	301 (25.1%)	191 (15.7%)
30	222 (45.3%)	215 (37.8%)	190 (40.9%)	210 (33.0%)
45	234 (64.6%)	257 (58.6%)	200 (57.4%)	203 (54.4%)
60	172 (78.8%)	190 (73.9%)	159 (70.5%)	203 (71.2%)
120	77 (85.3%)	94 (81.5%)	102 (78.8%)	(77 (77.5%)

The data were analyzed using generalized estimating equations (GEE) for ordered categorical outcomes, accounting for multiple episodes for each participant. The final model used included factors for treatment group, investigator site, and pretreatment heartburn severity. All tests were two-tailed, and statistical significance was accepted if the p-value rounded to three decimals was less than or equal to 0.050 *(Volume 14, pages 2957-9)*. For the above finding on time to onset of adequate relief of heartburn episodes, the model showed:

COMPARISON OF TREATMENTS FOR RAPIDITY OF ONSET OF ADEQUATE RELIEF

Treatment Comparison	*Model-Adjusted Odds-Ratio (95% C.I.)*	*Chi-Squared*	*p-value*
FACT vs FCT	1.34 (1.07, 1.69)	6.46	0.011
FACT vs antacid	1.28 (1.01, 1.63)	4.12	0.042
FACT vs placebo	1.61 (1.29, 2.01)	18.13	<0.001
FCT vs antacid	0.95 (0.75, 1.21)	0.15	0.702
FCT vs placebo	1.20 (0.97, 1.49)	2.77	0.096
Antacid vs placebo	1.26 (1.00, 1.58)	3.84	0.050

Inspection of the findings reveals that the FACT preparation was significantly more rapid acting than FCT, much better than placebo, and even slightly but significantly better than antacid, even as soon as 30 minutes after dosing. By 45 minutes and 60 minutes the advantage of antacid over placebo was fading, and the plain famotidine (FCT) after 45 minutes began to surpass the antacid. The FACT treatment remained better than any of the other three preparations at all time points and in the overall analysis using the GEE model.

Duration of effect was analyzed by adequate relief for at least 7 hours, 6, 5, 4, <4 hours, or none.

NUMBER AND (CUMULATIVE %) EPISODES ADEQUATELY RELIEVED IN 1231 PARTICIPANTS TREATED

	FACT	FCT	antacid	Placebo
adequate relief	n = 305	n = 311	n = 308	n = 307
for (hours)	*1205 episodes*	*1229 episodes*	*1212 episodes*	*1217 episodes*
≥7	845 (70.4%)	842 (68.3%)	741 (61.3%)	718 (59.0%)
6	20 (72.0%)	19 (69.8%)	14 (62.4%)	22 (60.8%)
5	28 (74.3%)	29 (72.2%)	30 (64.9%)	43 (64.3%)
4	26 (76.5%)	31 (74.7%)	41 (70.5%)	48 (68.2%)
<4	152 (89.0%)	142 (86.2%)	180 (83.2%)	182 (83.2%)

The model-adjusted comparisons of the treatments showed that antacid and placebo were not significantly different in duration of adequate heartburn relief (p = 0.579), nor were FACT and FCT (0.366). The FACT product was significantly better than antacid or placebo, and FCT was also longer acting than antacid or placebo.

COMPARISON OF TREATMENTS FOR DURATION OF ADEQUATE RELIEF

Treatment Comparison	*Model-Adjusted Odds-Ratio (95% C.I.)*	*Chi-Squared*	*p-value*
FACT vs FCT	1.11 (0.89, 1.39)	0.822	0.366
FACT vs antacid	1.49 (1.19, 1.87)	11.73	0.001
FACT vs placebo	1.59 (1.28, 1.97)	17.37	<0.001
FCT vs antacid	1.34 (1.07, 1.68)	6.61	0.010
FCT vs placebo	1.43 (1.15, 1.77)	10.78	0.001
Antacid vs placebo	1.06 (0.86, 1.32)	0.31	0.579

When the primary comparisons were made for proportions of participants who showed both rapid onset and long duration, mainly for FACT vs FCT, and FACT vs antacid. The FACT product was especially better than FCT at 15 minutes, and especially better than antacid after 15 minutes, and much better than placebo at all time points. A "successful" treatment of a heartburn episode was prompt relief within an hour that was sustained for 8 hours post-dose and no rescue antacid was required.

HEARTBURN EPISODES SUCCESSFULLY TREATED BOTH PROMPTLY AND FOR 8 HOURS

	FACT	FCT	antacid	placebo
adequate relief	n = 305	n = 311	n = 308	n = 307
at (minutes)	*1205 episodes*	*1229 episodes*	*1212 episodes*	*1217 episodes*
15	244 (20.6%)	185 (15.0%)	184 (15.4%)	109 (9.0%)
30	428 (35.8%)	370 (30.1%)	322 (39.6%)	269 (22.2%)
45	609 (50.7%)	559 (45.4%)	476 (39.6%)	445 (36.6%)
60	738 (61.4%)	703 (57.0%)	603 (50.1%)	591 (48.6%)

Comparing FACT and FCT (for promptness, especially) and FACT and antacid (for duration, especially),

adequate relief at	*Treatment Comparison*	*Model-Adjusted Odds-Ratio (95% C.I.)*	*Chi-Squared*	*p-value*
15 minutes	FACT vs FCT	1.47 (1.08, 2.02)	5.85	0.016
	FACT vs antacid	1.40 (1.01, 1.94)	4.08	0.043
30 minutes	FACT vs FCT	1.30 (1.00, 1.68)	3.89	0.048
	FACT vs antacid	1.49 (1.14, 1.95)	8.57	0.003
45 minutes	FACT vs FCT	1.24 (0.98, 1.56)	3.21	0.073
	FACT vs antacid	1.55 (1.22, 1.98)	12.87	<0.001
60 minutes	FACT vs FCT	1.20 (0.95, 1.51)	2.32	0.128
	FACT vs antacid	1.58 (1.25, 2.00)	14.59	<0.001

Comment: Note that FACT loses its advantage over FCT after 30 minutes, when the longer-duration effects of famotidine become predominant, and that FACT is not much better than antacid at the 15-minute point but much better thereafter. FACT is far better than placebo at all time points and FCT is also better than placebo at all time points. Antacid is better than placebo only at 15 minutes, and neither of them have long duration of effect.

Episodes for which rescue antacid tablets were taken showed similar results:

NUMBER AND (CUMULATIVE %) EPISODES REQUIRING RESCUE ANTACIDS

	FACT	FCT	antacid	Placebo
use of rescue	n = 305	n = 311	n = 308	n = 307
antacid tablets	*1205 episodes*	*1229 episodes*	*1212 episodes*	*1217 episodes*
<1 hour	35 (2.9%)	46 (3.9%)	48 (4.0%)	45 (3.8%)
1 to <2 hours	70 (8.6%)	90 (11.4%)	101 (12.2%)	107 (12.5%)
2 to <4 hours	98 (16.7%)	108 (20.2%)	141 (23.8%)	135 (23.6%)
4 to <6 hours	55 (21.2%)	73 (26.1%)	69 (29.6%)	102 (31.9%)
6 to <8 hours	47 (25.1%)	31 (28.6%)	34 (32.4%)	51 (36.1%)
none used	900	881	819	777

FACT was significantly ($p = 0.004$) better than antacid, very much better than placebo ($p < 0.001$) and FCT was better than placebo ($p = 0.013$), but the other treatment comparisons showed no significant differences. There were no serious safety problems with FACT, although one participant after FCT was found to have an ovarian cyst thought unrelated to study drug, and one participant after placebo developed vomiting and hospitalization revealed esophagitis probably unrelated. One participant quit the study after taking antacid because of sinusitis, and another after FCT quit because of abdominal pain.

Comment: This very large study of over 4800 heartburn episodes appeared to show clinically useful and statistically significant differences between FACT and FCT in promptness of effect at 15 and 30 minutes, and between FACT and antacid in duration of effect, as was postulated to be proved. The differences in this study were somewhat more impressive than in the earlier studies, in part because of the very large number of episodes treated. This study did not focus on a specific meal that might provoke nocturnal symptoms, and in fact most of the episodes were experienced during the waking day. Nevertheless, both rapidity of effect and long duration of benefit were shown by this study design. The endpoint of participant-determined adequate relief of heartburn did not require participant grading of symptom severity, and had been a more difficult criterion to meet in the earlier studies than reduction of heartburn severity by at least one grade.

It was apparent that the sponsor was learning from previous studies how to design and evaluate later studies, so that by the time of Study 110 some of the arbitrary and artificial features of the earlier studies had disappeared. Study 109 had been disappointing in the failure to demonstrate statistically significant reduction in nocturnal waking with heartburn, even though a consistent and strong trend was seen. This was attributed to design flaw, since the provocative meal was given early, and no provocative bedtime snack was given, as in the pilot study. The final study of multiple episodes of heartburn during active hours was closer to clinical reality of how participants might behave, and provided evidence of the advantage of the new FACT.

C. Supplemental use study

1. Study 111: open-label, multiple-dose, pattern of use

The last of the submitted clinical studies, Study 111, was a more modest-sized study of how participants might actually use a drug product such as FACT (formulation C-675-8C, the same as used in the several studies summarized above). It was coordinated by ——— ——— who worked with physicians at 10 shopping malls geographically dispersed through the United States, 2 of which were her own workplaces *(Volume 15, page 3824)*:

List of Shopping Malls and Subinvestigators

Study participants were recruited from mall shoppers who were adults at least 18 and who used either antacids or OTC acid reducers at least twice monthly for relief or prevention of heartburn. They also had to have expressed positive or neutral interest in possibly purchasing a new product such as FACT ("definitely would buy," or "might or not buy"), consent after the protocol was explained, and if female not be or become pregnant. Participants eligible were given 30 tablets of the new famotidine 10 mg-antacid 21 mEq ANC-chewable tablet product (formulation C-675-8C, the same FACT product used in the previous studies).

They were to use the chewable tablets, called "Advanced PEPCID AC," over the subsequent 2-week period, as directed on the label on the box containing the product. The advertising on the test package stated:

"If you suffer from heartburn or acid indigestion, you want both *fast acting* and *long lasting* relief. New ADVANCED PEPCID AC is the only heartburn medicine that gives you both.

"ADVANCED PEPCID AC is specially formulated so it begins to work immediately. And nothing lasts longer than ADVANCED PEPCID AC. In fact, you can take it after a meal, and 12 hours later it's still controlling acid.

"ADVANCED PEPCID AC – the *fast acting, long lasting* heartburn medicine. In chewable tablets."

The instructions for use of the product were as follows *(Volume 15, page 3726)*:

USES

- For Relief of heartburn, acid indigestion, and sour stomach.

DIRECTIONS

- For **Relief** of symptoms **chew 1 tablet thoroughly and swallow with** water.
- Do not use with other acid reducers.
- Can be used up to twice daily (up to 2 tablets in 24 hours).
- This product should not be given to children under 12 years old unless directed by a doctor.

WARNINGS

- Do not take the maximum daily dosage (2 tablets) for more than 2 weeks continuously except under the advice and supervision of a doctor.
- As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.
- If you have trouble swallowing, or persistent abdominal pain, see your doctor promptly. You may have a serious condition that may need different treatment.
- Keep this and all drugs out of the reach of children.
- In case of accidental overdose, seek professional assistance or contact a poison control center immediately.

DRUG INTERACTION PRECAUTION

- 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.

READ THE LABEL

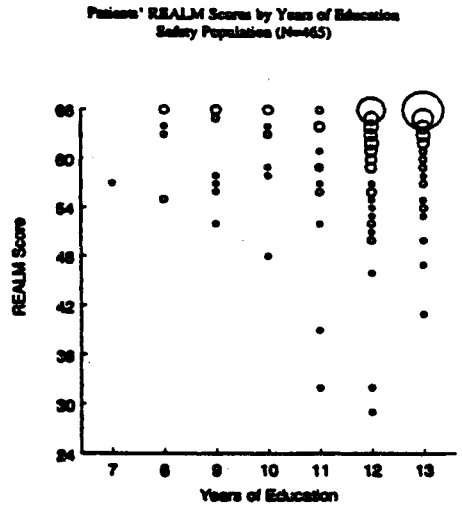
- Read the directions and warnings before use.
- Keep the carton and package insert. They contain important information.

It was intended to survey use patterns in 50 people at each site, or 500 in all. The size of the study was based on needing a sample of 400 to give 95% confidence intervals of ± 9.8% in true percentages of participants who took more than 2 tablets on any given day in the study period, or took more than one tablet at a time at least once during the study period.

Prospective participants at each mall were escorted by an interviewer to a field agency office at the mall, where a study nurse asked for medical history to determine eligibility, explain the

study, and obtain informed consent. Participants listed what antacids or acid reducers they had been using, and completed a reading test (Rapid Estimate of Adult Literacy in Medicine, REALM, Davis, et al., 1993; *Volume 15, pages 3666-70*). The test consisted of three lists of 22 words each, on a card that was given to the participant to assess reading recognition of lay medical terms, from very simple to somewhat increased difficulty. Words correctly recognized and pronounced were scored, and the results converted into reading level grades of $\geq 9^{th}$ (61-66 correct), 7^{th}-8^{th} (45-60), 4^{th}-6^{th} (19-44), and 3^{rd} or below (0-18 correct).

As executed, 496 people entered the study and each was given 30 tablets of the new FACT product. Their ages ranged from 18 to 80, and there were 272 (54.8%) women. Of the 496, 31 took no study medication, leaving 465 as the "safety" population sample. Of the 465, most of the people had education beyond high school and the median REALM score was 66, but of course half the participants had lower values ranging down to 29 (one had a score of 1).



Of the 465 participants, 88 did not cooperate further and were lost to follow-up, but 377 said they did take study medication at least once, but 4 did not turn in diary cards, leaving 373 for whom data were available ("all-participants-treated"). Of the 373 who submitted diaries, 285 had diaries that matched the number of tablets returned, 69 did not match, and 19 turned diaries but no tablets. Of the 373, 313 took one tablet or less per exposure day, 57 more took more than 1 but no more than 2 tablets per day, and only 3 exceeded the 2-tablet limit for average consumption. Results of the study suggested *(Volume 15, pages 3646-7)* that about 76% of the people who were studied used FACT as instructed, 89/373 did not always do so. Of them 84 took more than 1 tablet per dose at least once during the study, and 31 took more than 2 in one day (some did both), and 18 people took from 4 to 6 tablets on at least one day. None took more than 6 tablets (60 mg of famotidine) in a day. The REALM testing indicated that the mean reading score was 63.7 out of a possible 66, but did not test comprehension of what was read. The noncompliant people had median educational levels of 12 years, compared to 13 years in the compliant participants who followed instructions.

Comment: This study was an attempt to assess what people really do, although the study participants were self-selected sample, and may or may not represent the actual consumers.

IV. Integrated Summary of Effectiveness

In order to demonstrate effectiveness of the new chewable famotidine-antacid combination tablet, referred to throughout this document as the FACT product, the sponsor has constructed a body of evidence in support of two maj . points:

1) the new FACT had to be proved significantly superior to famotidine 10 mg alone in its rapidity of clinical benefit, and
2) the FACT product had to be significantly longer acting than antacid alone.

At the same time, it was necessary to show that putting the antacid and famotidine together in a single chewable tablet would not impair or significantly reduce the effectiveness of the antacid component nor the duration of effect of the famotidine.

Comment: The intended use for which the product is to be marketed if approved is for relief of heartburn, especially that induced by certain food or beverages that individuals have found by experience often induce such symptoms. The consumption of the FACT product is mainly aimed at taking it after symptoms have been induced by some individually provccative meal or combination of food and drink. The disintegration, dissolution, and rapidity of intragastric neutralization of acid, and of absorption of the famotidine after chewing and swallowing a FACT were critical features in predicting probably clinical effects. The clinical benefit of prompt and sustained relief of the heartburn, however, could only be assessed by the people who had the symptoms, regardless of surrogate, predictive measures of acid-neutralizing capacity (ANC) or pH in the stomach cavity or esophagus, or of blood levels of famotidine.

Concerns have been raised about the more rapid absorption of FCT than FACT and differences in Cmax and Tmax, and the intragastric pH drop following the meal and antacid effects abate after two hours. This product is intended for use by consumers to relieve heartburn that begins usually after a meal of some provocative food or drink. It is not intended as a fasting preventative medication. The data on FACT vs FCT after a meal show almost identical absorption and pharmacokinetics for blood levels of famotidine. It is of little or no clinical concern that FACT, which is chewed, wet with saliva, then swallowed with water, may deliver the famotidine a little less rapidly for absorption than does the OTC tablet of famotidine 10 mg because of the alkalinization effect of the antacid in the FACT. The slight reduction in Cmax is of no clinical concern, since the range of famotidine dosing has a wide margin of safety.

It was not easy to show efficacy in these studies, and the high numbers of participants who showed placebo responses was a problem throughout all of them. The end points were entirely subjective and not easy to quantitate or interpret. Because so many of the participants appeared to show spontaneous abatement of heartburn symptoms (placebo effect), and inconsistent responses to the provocative meals, there was a great deal of "noise" in these studies. The advantages of the FACT product over the test antacid product or marketed FCT product used in these studies as comparators were small, and it required large numbers of participants and of heartburn episodes to show statistically significant benefits. Of the three large clinical trials, Studies 106, 109, and 110, only the last is convincing of the statistically significant efficacy of the FACT over either antacid or famotidine alone.

Study 106 is a difficult design to interpret, since it is a hybrid of both relief and preventative effects. The timing of the test medications to treat "spontaneous" heartburn during the day (unclear whether it may have followed either breakfast or lunch) and then four hours later to eat a meal considered by the individual participant to be "provocative" is a confusing design. The results showed only scattered measures of efficacy that were significant: FACT significantly more rapid in adequately relieving spontaneous daytime heartburn than FCT at 30 minutes after dosing (7.1%, p = 0.042) and 45 minutes after dosing (10.2%, p = 0.010). It was slightly but not significantly better than antacid at 15, 30, and 45 minutes after dosing (but that was not required to be demonstrated). Duration of adequate relief was not assessed in this study, and was confused by the intervening "provocative" meal at 4 hours after dosing.

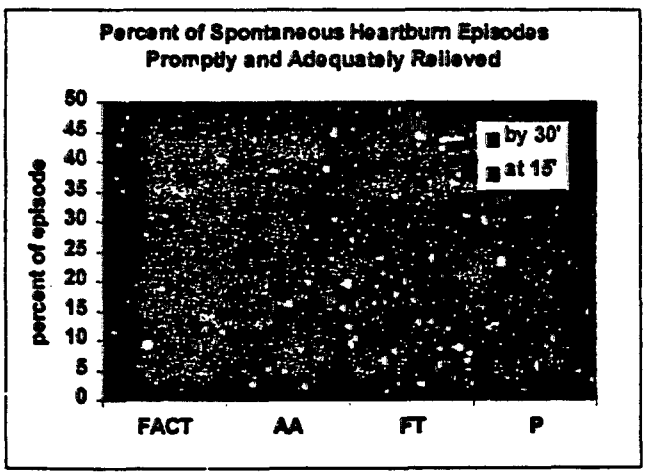
Study 109, the evening "provocative meal" study, also produced some but not consistently positive results indicating significant efficacy. The provocative meal of onion-cheese seasoned chili and iced tea was not uniformly provocative as a stimulus of heartburn (386 of 1525 patients or participants, 25.3%, did not develop sufficient heartburn symptoms and were not randomized to be treated). Time to adequate relief was significantly shorter for participants taking FACT than for those taking FCT, by about 20 minutes for the median and 95% confidence interval, but the placebo results were not significantly worse than the FACT results although the median and confidence intervals were the same as for the FCT product. For at least one grade reduction in severity of heartburn at 30 minutes, the participants taking FACT showed significantly better results than those taking either famotidine (+13.0%, p =0.002) or placebo (+9.9%, p = 0.017), but not significantly better than antacid (+3.7%, p =-0.38). For duration of benefit, assessed by no awakening during the night after the provocative meal, FACT was significantly better than placebo both in the ITT and per-protocol analyses, better than antacid only in the per-protocol analysis, and not significantly better than famotidine in either analysis, as expected.

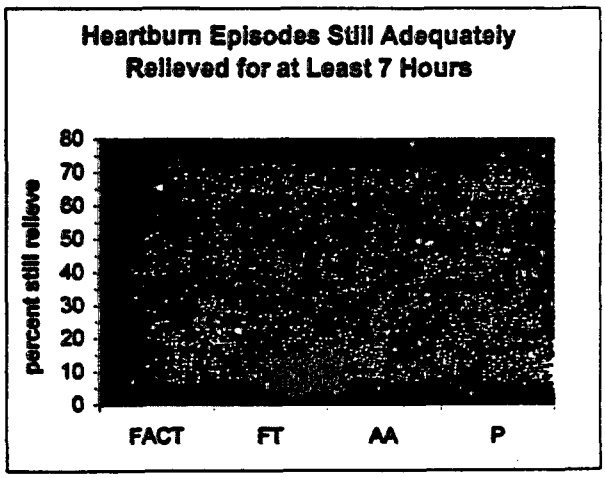
The expected results seemed finally to be achieved in Study 110, after the weak and equivocal results in Studies 106 and 109. Study 110 did not depend on a provocative meal, but dealt with persons who had a history of food-induced heartburn at least three times per week over the recent two months, of sufficient severity to require taking antacids or OTC acid reducers for relief. Each participant was instructed to self-treat four episodes of heartburn of that severity, using study medication, and to record whether adequate relief was obtained at 15, 30, 45, 60, or 120 minutes, and whether the symptoms recurred within 4, 5, 6, or 7 hours. Data on 4963 episodes in 1240 participants were obtained, showing significantly more heartburn episodes adequately relieved at 15 minutes by FACT than by famotidine alone (+6.4%, p = 0.0001) or by placebo (+11.0%, p << 0.0001) but not significantly better than antacid (+1.8%, p = 0.233). The duration of adequate relief was at least 7 hours in significantly more who had been relieved by FACT than by antacid (+5.2%, p = 0.005) or placebo (+8.0%, p = 0.00002) but not significantly more than famotidine (+0.7%, p = 0.433). When adequate relief both at 15 minutes and for at least 7 hours was considered, significantly more participants taking FACT than famotidine alone (+5.2%, p = 0.0007) or antacid alone (+5.1%, p = 0.0011) or placebo (+11.3%, P <<0.00001) were found. This study, the one with the fewest design flaws, was the most unequivocably positive in fulfilling the criteria set for justification of the combination product. This study alone was not sufficiently compelling to justify approval, since there may be some statistical concerns about the GEE method, and the incremental clinical benefit of the FACT product over famotidine or antacid alone is only marginal.

The question about the peppermint/spearmint content of the FACT product contributing to possible relaxation of the lower esophageal sphincter cannot be answered by the data of these studies. The FACTs contain — mg of peppermint flavoring [redacted] and the antacid and placebo comparator tablets each contained — mg of the same peppermint plus 1 mg of [redacted] as flavoring. The famotidine tablets, as marketed for simple swallowing with water, contained no mint flavoring. To what extent this might have affected the results of these studies cannot be answered, for the question was not asked. If anything, the mint could possibly have worsened the effects of FACT relative to famotidine alone (but did not as observed), and would have roughly comparable effects if any to the antacid and placebo. Peppermint was used in the 18th century for treatment of dyspepsia and for what we now call irritable bowel syndrome, as a stomachic, carminative agent, but mostly for moderating the bad taste of unpleasant medicines (Millspaugh, 1892). At present, it is recognized as a dietary constituent that perhaps should be avoided in people with gastroesophageal reflux disease and heartburn symptoms (Ogorek, 1995). It is the opinion of this reviewer that any effects of the mint flavoring were probably negligible and did not affect the results to any detectable extent.

Labeling Considerations

If it is decided that this combination product should be approved, despite this reviewer's recommendation that a confirming study is needed, then labeling considerations are important. The requested labeling includes two bar graphs that compare the FACT product to placebo, taken from the results of Study 110 for adequate relief within 30 minutes and duration of relief for at least 7 hours (Volume 14: page 2976, Table 13 and page 2979, Table 14). It is this reviewer's opinion that these comparisons are inappropriate, since the question the consumers will have is not whether the FACT is better than nothing, but whether it is better than either the famotidine or antacid alone. Therefore it would appear to be far more appropriate to compare the results with those obtained in that study with those agents, as shown below:

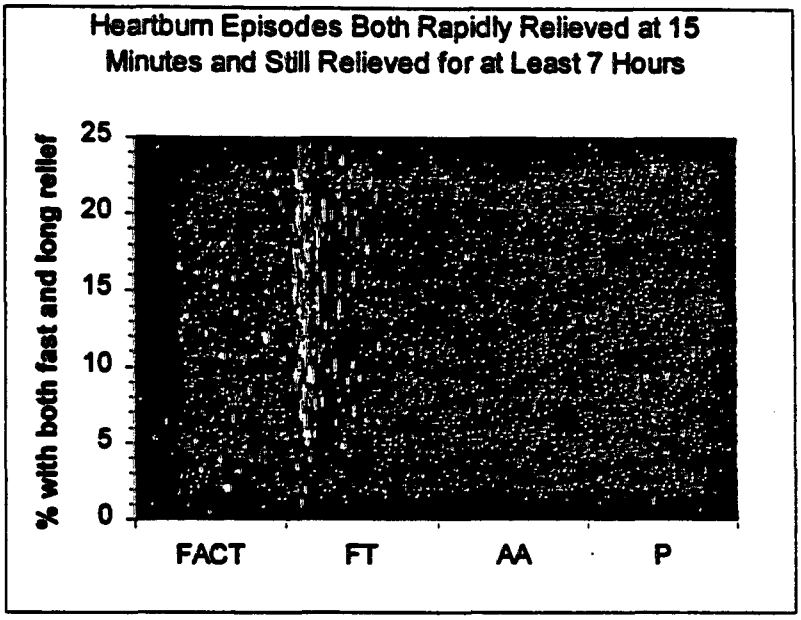




In the left bar-graph above the results of adequate relief at 15 minutes are shown in the lower portion of each bar, and the increments at 30 minutes above, so the total bar represents the sum

of both, for each treatment group. The FACT and antacid are comparable at 15 minutes, and significantly better than either famotidine alone (FT) or placebo. By 30 minutes, the cumulative proportions of adequately relieved episodes are significantly better for those treated with FACT than any of the other three products. On the right, the duration of adequate relief by FACT is comparable to and not significantly different from famotidine tablets (FT), and both are significantly better than antacid or placebo.

For both rapid relief in 15 minutes and prolonged duration of relief for at least 7 hours in the same episodes in the same persons:



The FACT product was better than antacid (because of better prolongation) or famotidine (because of faster onset), and all three were better than placebo, as shown above. These simple bar graphs show the actual data in a clear and easily understood manner. It is evident that the differences are relatively small, and the advantages of the new FACT product are modest gains over famotidine alone and antacid alone, even though they may be statistically significant mainly because of the very large numbers of heartburn episodes treated in Study 110.

Other labeling concerns may be considered, as to whether the magnesium content of the FACT product should be of concern, and whether absorption of antacids such as tetracycline may be impaired. The FACT product is intended to be taken one at a time, and no more than two per day. Each FACT contains only 5.7 mEq of magnesium hydroxide and only 21 mEq of total antacid. This is much less than the commonly used doses of ordinary antacids such as Maalox Extra Strength Suspension, the recommended dose of which is 2 to 4 teaspoonfuls, or 59.6 to 119.2 mEq of ANC and 31 to 62 mEq of magnesium hydroxide. Nevertheless, the standard warnings about use in persons with kidney disease and who require certain medications may still be worth including, to keep on the conservative side.

V. Integrated Summary of Safety

Comment: It was not expected that there should be a safety problem in these studies, since the drug materials given were mainly in single, intermittent doses of already approved OTC products. Antacids containing $CaCO_3$ and $Mg(OH)_2$ in amounts of 800 mg and 165 mg per tablet, respectively, are considered very safe, as described in the Antacid Monograph (21 CFR Part 331: 223-7). Famotidine 10 mg tablets are approved for OTC use as PEPCID® AC. The placebo antacid chewable tablets and placebo famotidine tablets contained only components generally recognized as safe. It was therefore not to be expected that combining the two OTC components of antacid and famotidine 10 mg in a single chewable tablet, to be used no more than twice a day, would generate safety problems of any magnitude or severity. Further, in these studies, either healthy subjects or heartburn sufferers who did not have other serious medical illnesses were included.

A. Extent of exposure in these submitted studies

A total of 4485 individual participants received study medication in these clinical trials, 87 of whom were in crossover studies. The number of people who received the FACT preparation was 1519, famotidine 10 mg tablets 1064, antacid tablets 995, and placebo. Most of the people received only one dose and none more than four doses. In the studies designated as "primary" by the sponsor *(Volume 9:53)*, comprising 3893 participants in Studies 104, 106, 109, 110, there were 38% men and 62% women, and 83% were Caucasian. Their mean age was 40.8 years, ranging from 17 to 88.

B. Adverse clinical and laboratory events in these studies

Considering all 4485 people, there were only 259 (5.7%) with any adverse event, and no difference in incidence by treatment group. For those receiving FACT 5.5%, FCT 5.7%, antacid 6.5%, and placebo 5.0%. Headaches were the most common complaint, with diarrhea a distant second. Again there were no significant differences in incidence between the treatment groups.

C. Serious adverse events in these studies

There were no deaths in these participants and volunteers, and only 3 serious events. Of the latter, none were in people taking FACT, but one woman on FCT had an ovarian cyst, one on antacid had acute gastroenteritis, and one on placebo had esophagitis and vomiting.

D. Drug-drug interactions in these studies

None were identified. Antacids are well known to interfere with absorption of several drugs, but that was not investigated in these studies. No studies were done to characterize any possible interactions with the components of the FACT tablets.

E. Comparisons with post-marketing safety experience

The combination FACT preparation has not been marketed.

VI. Summary of Benefits, Risks of the Proposed Formulation

The new FACT product appears to have fulfilled partially its aims as being an acceptable, easily chewable tablet with prompt efficacy in providing adequate relief of meal-induced heartburn, significantly faster than pro.ided 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 appears to have sustained adequate relief for at least 7 hours that is significantly superior to the antacid (or placebo) and at least as good as famotidine alone. These features are what the sponsor set out to prove, in formulating the FACT product, testing it biopharmaceutically and in several large clinical trials. Since only Study 110 is convincing, it is suggested that a confirming study should be done, using a similar design. There were no clinically significant risks of the FACT product, used as directed in the proposed OTC labeling, or even if somewhat misused by consumers up to 6 tablets/day (60 mg of famotidine.

VII. Regulatory Recommendations

Of the three major clinical studies done in support of this application, only one is persuasive. Study 106 failed to show a significant prompt effect on relief of daytime heartburn, and Study 109 failed to show a significant advantage over antacid in duration of effect in prolonged relief of meal-induced evening heartburn. Only Study 110 shows convincingly that the new FACT product is significantly more rapid in its providing adequate relief of heartburn symptoms than does famotidine 10 mg alone, and is significantly longer acting than 21 mEq of antacid alone. This reviewer finds the evidence of clinical effectiveness not sufficiently persuasive that Study 110 alone can justify approval, since the incremental clinical benefit of the combination product is marginal, and some serious statistical questions have been raised (see Statistical Review).

It is recommended that a confirming study should be done, perhaps avoiding the problems of analyzing multiple episodes in the same persons. Therefore, approval of this product is not recommended until a confirming study has been done and reviewed.

/S/ 21 Jan '99

John R. Senior, M.D., Medical Officer — date
Division of Gastrointestinal & Coagulation Drug Products

cc:
NDA 20-958
HFD-180
HFD-180/LTalarico /S/ 1-22-99
HFD-180/HGallo-Torres
HFD-180/JSenior
HFD-180/JChoudary
HFD-180/WMAdams
HFD-870/ARSancho
HFD-720/MMRashid
HFD-181/CSO
HFD-180/EDuffy
f/t 1/22/99 jgw
N/20958901.0JS

Concur. January 22, 1999

/S/

VIII. References

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CSO/Folkendt

MEDICAL OFFICER REVIEW
Division of Over-The-Counter Drug Products

NDA # 20-958
Name: Pepcid AC®Advanced Acid Reducer/Antacid Tablets (famotidine 10mg/calcium carbonate 800mg/magnesium hydroxide 165mg)
Sponsor: Johnson & Johnson *Merck Consumer Pharmaceuticals Co.
Type of Submission: Original NDA
Date of Submission: 12/23/97
JAN 13 1999
Date of Review: 11/30/98
Reviewer: Andrea Leonard-Segal,M.D.

MK-0208C: An Open-Label Study to Evaluate the Patterns of Use of Famotidine/Antacid Combination Tablets In Patients Who Use Antacids or OTC Acid Reducers. Protocol No. 111.

Background

The following actual use study has been submitted in support of famotidine/antacid combination tablets (FACT) that combine famotidine 10mg, calcium carbonate 800mg, and magnesium hydroxide 165mg in a single chewable tablet. This tablet, developed by Johnson & Johnson*Merck Consumer Pharmaceuticals Co., is designed to offer both rapid relief of heartburn, acid indigestion and sour stomach from its antacid component and longer duration of relief from its famotidine component. The antacid component of the tablet provides 21 mEq of acid-neutralizing capacity, similar to other OTC antacid products. The purpose of Protocol 111 was to investigate whether patients who use antacids or OTC acid reducers would take FACT as directed on the product label.

Study Objective

The objective of the study was to evaluate the patterns of use of FACT among consumers who indicate a positive or neutral purchase interest in the product based on the product concept.

Trial Design

This was a multicenter, open-label, 2-week home-use study. Consumers were recruited and enrolled from 10 shopping malls in geographically dispersed sites. At a field agency within each mall, patients were screened for inclusion and exclusion criteria. To determine eligibility, a nurse reviewed patients' medical histories. Each patient listed what antacids and /or OTC acid reducers he/she currently used and completed a Rapid Estimate of Adult Literacy in Medicine (REALM) test to determine reading ability.

Included:

1. Age 18 or over.
2. Antacids or OTC acid reducers used at least twice per month.
3. Expressed positive or neutral purchase interest after reviewing the product concept.
4. Signed written informed consent after the nature of the study was explained and before beginning the protocol.
5. (Females Only) Used adequate means of contraception and refrained from becoming pregnant during the study.

Excluded:

1. Participated in a research study within 30 days prior to study start.
2. Taking oral tetracycline.
3. History of known renal impairment.
4. Self-reported pregnancy or lactation.
5. History of prior adverse reaction to any OTC or prescription H2 receptor antagonists.

Once included, volunteers were provided with one bottle of 30 FACT on which their initials were written. They were also given a product label that told them what the drug was and how to use it. They were instructed to use the product as directed on the label over a two-week period at home. They were told to return all unused medication and packaging at the end of the study. Diary cards for recording date, hour and minute, # of FACT taken, and the date, hour and minute, of other heartburn medication taken, were provided to each patient for a record of medicating. Volunteers were given a toll-free pager number and told to call with any unexpected events that occurred during the study period, or with any questions. Adverse experiences were documented on the diary cards even though there was no specific section designated to record them. An investigator from Walker Clinical Evaluations (WCE) followed up on all adverse events. Physicians in each geographic area were available to follow-up, if needed. Adverse events were recorded on an Adverse Experience Case Report Form by the investigator and were rated as to intensity (mild, moderate, severe), seriousness, action taken relationship to test drug, and duration. There were no laboratory tests conducted for the evaluation of safety. Volunteers were given preaddressed, stamped envelopes for returning diary cards, unused medication, and packaging to WCE at the end of the study.

Results

Four hundred ninety-six consumers (224 males and 272 females) entered the study. The age range was 18-80 years. The volunteers were 86.3% Caucasian and 10.6% Black, with small percentages of other races represented. They complained of a broad range of secondary diagnoses, or conditions, the most common of which are presented in order of frequency: hypertension, headache, diabetes, arthritis, depression, hypothyroidism, hypercholesterolemia, allergies, and asthma.

Thirty-one volunteers (including two who withdrew from the study) did not medicate with the study drug and were not included in any of the patterns of use or safety analyses. Of the remaining 465 volunteers, 57.2% took medication for their secondary diagnoses and for heartburn within one week prior to entering the study. Thirty-nine of these volunteers were on nonsteroidal antiinflammatory drugs (NSAIDS). Thirty-one were on aspirin containing compounds. Eighty-five volunteers (18.5%) were taking gastrointestinal drugs including a variety of antacids, acid reducers, and anti-flatulants. Fifteen volunteers were already on famotidine and 22 were on calcium carbonate.

Seventy-two volunteers, of the 465 (15.5%), reported using concomitant medication. None reported taking NSAIDS. Two took aspirin containing compounds. Sixty-seven (14.4%) took gastrointestinal drugs including 26 patients who took calcium carbonate, 2 who took famotidine, 5 who took cimetidine, 1 who took nizatidine, and 8 who took ranitidine.

The mean REALM score was 63.7 out of a possible 66, equating to a reading level of 9th grade or above. This was consistent with the reported education levels for study participants. The study population did not include any volunteers with less than 7 years of education.

Of the 465 volunteers, 88 were lost to follow-up but are included in the safety analyses as if they took test medication and did not report any adverse experiences. One did not fill out her diary; two did not return their diary cards; one did not return the diary card but returned 29 tablets so it was assumed she took one dose.

Three hundred seventy-three volunteers, referred to as "all-patients-treated," were included in the analysis of patterns of use (465 minus the 88 lost to follow-up patients). Volunteers who discontinued for reasons such as adverse experiences or ineffective therapy were included in this analysis. Twelve of the 373 recorded some or all of their doses on the diary with dates that preceded the date they received the study medication. All doses for these volunteers were included in the analyses and were handled the same as all other doses. Of the 373, 285 (76.4%) returned tablets to match what was written on the diary. Sixty-nine (18.5)% had diaries that did not match the number of tablets returned, but 43 of these volunteers' diaries were within 2 tablets of what should have been recorded to account for all 30 tablets. (The sponsor felt that since there were diaries with tablet counts that over- and under-reported use, and the majority of these counts were within 2 tablets, the differences would not seriously affect the inferences drawn from the trial.) Nineteen (5.1%) volunteers returned diaries but no tablets.

The sponsor noted that some volunteers did not return items promptly at two weeks, which might have provided them the opportunity to take study medication for a longer period, thus, translating into volunteers having different time on study medication. To account for each person's actual treatment period, the total number of exposure days was calculated to represent the number of days from the day a patient received study medication until the day he/she took the last dose. For the 12 people who recorded dosing dates that preceded the date they received study medication, the number of exposure days was calculated as the number of days from the first day of dosing until the last. The number of treatment days ranged from 1 – 23 with 92.8% treating for 14 days or less. The total dose of study medication taken throughout the study period ranged from 1 tablet to 32 tablets. (The sponsor noted that one volunteer reported taking more than the 30 tablets that were supposed to be in the medication bottle.)

Volunteers who took one tablet per dose either once or twice per day were considered compliant. They were considered to be noncompliant if they a) took more than one tablet per dose, or b) took more than two tablets per day, or c) did both of these things. Two hundred eighty-four (76.1%) of the 373 volunteers were considered to be compliant. Eighty-nine (23.9%) of volunteers were considered to be noncompliant, 26 of whom were considered to be noncomplaint for both reasons. Eighty-four (22.5%) volunteers took more than one tablet per dose at least once; one of these took 4 per dose on each of two days and one took 3 per dose on each of three days. Thirty-one (8.3%) took more than 2 tablets on at least one day during the study period. Eighteen (4.8%) took 4-6 tablets on at least one day, up to 60mg of famotidine. No one took more than 6 tablets in one day.

The number (%) of all volunteers who took >1 dose/day at least once was 139/373 (37.3%). Regarding the spacing of these multiple doses, 6.5% of volunteers took more than one tablet within the first hour of taking the original dose, 7.9% between hours 1-2, 5.8% between hours 2-3, and 12.9% between hours 3-4. 72.7% of patients took a second dose >8 hours after the original dose.

Nine people (1.9%) reported at least one adverse experience. These 9 were complaint with dosing instructions. Seven of the nine experienced a drug-related adverse event. Two (0.4%) discontinued the study drug due to a clinical adverse experience. One of them had constipation and the other had nausea plus taste-perversion. There were no volunteers who reported a serious event.

MEDICAL OFFICER COMMENTS:

1. Population issues:

The original protocol calls for subgroup analyses of REALM score groups ≤ 44 or >44. The study population did not reflect a wide cross section of reading ability, so the subgroups were revised upward to assess people with a REALM scores ≤ 60 and between 61-66. Study results, therefore, may not accurately reflect the ability of the general population to use the drug properly.

After reviewing the product concept, people who indicated that they probably or definitely would not buy FACT were excluded from the study. We do not know why these people had a negative response to the product, and whether this really translates into a predictor for who would buy the product from a drug store.

The inclusion criteria form did not ask female patients to specify what kind of birth control they were in fact using. It is not clear, therefore, that women in the study in fact were using "adequate" birth control.

Individuals with active peptic ulcer disease and other serious gastrointestinal disorders were permitted to enter the study. There should have been investigator follow-up at the end of the study to determine how individuals using concomitant medications did, looking at adverse events either due to the use of medications or worsening of the underlying condition being treated.

2. Labeling and Diary Issues:

A warning referring individuals with PUD and with other serious gastrointestinal conditions to consult their physicians before taking the OTC medication, would be medically sound to keep these patients under the active care of their physicians. OTC products such as iron, whose absorption may be impaired secondary to antacids, should also be considered as having potential problems with drug interactions. Consumers should be warned not to use this Pepcid product with other Pepcid products in order to avoid potential overdosing. The study label warns about a drug interaction with certain prescription drugs, but does not specify any (i.e. tetracycline). Thus it may be reasonable to include additional medication warnings.

The Clinical Pharmacology and Biopharmaceutics Review indicates that the half-life of famotidine is markedly increased in people with renal impairment. The OTC label should include a warning (as per Mylanta Gelcaps) about the danger of taking FACT if a person has kidney disease, both because of the antacid component and the famotidine component.

The Division of Drug Marketing, Advertising, and Communications comments that persons who who met exclusion criteria were not given the opportunity to choose whether or not to take FACT. Thus there is no data as to whether such persons would appropriately choose not to use the product if it were on the market. Asking all comers whether or not they could use the product, before implementing the exclusion criteria, would have given this data. The medicine label should list study exclusion criteria (tetracycline, renal impairment, pregnancy or lactation, history of adverse reactions to OTC or prescription receptor antagonists) as "warnings", because consumers with those conditions, unless specifically mentioned, would be using the product.

The accuracy of the pattern of use data recorded on the diary cards could be questioned, since the patients knew the cards would be reviewed. It is possible that inappropriate dosing was higher than recorded. Some patients may have skewed their entries to make themselves look compliant.

The diary was poorly constructed in that there was nowhere for volunteers to list why they took the study medication. When evaluating use, it is important to know whether volunteers actually took the medication for the indications on the label. Similarly, there was no space on the "Other Heartburn Medication" card for patients to say why they took those medications during study period.

3. Usage and Compliance Issues:

Many volunteers were taking prescription drugs while participating in the FACT study. We do not know if they consulted their physicians about this as the label instructed. This aspect of the compliance issue was not addressed. Also, we do not know the extent of prescription medication used during the study because there was no diary space to list any medication other than heartburn medication.

We do know there was concomitant use of other acid reducers and antacids during the study. Sixteen volunteers took FACT with other acid reducers despite the label warning against this. A review of the line list shows that several patients in the study took other acid reducers with FACT in the same 24-hour period (cimetidine, ranitidine, nizatidine) and some took additional antacids, bismuth subsalicylate and cisapride. Volunteers who did take acid reducers the concomitantly were noncompliant because they did not follow the label direction not to use other acid reducers.

The bioavailability of famotidine is increased in the presence of food and decreased with antacids. During the day, under fasting conditions, the Tmax of FACT at 2.4 hours is 35 minutes longer than for Famotidine Chewable Tablets (FCT) 10mg at 1.8 hours. The Tmax occurs well after the presence and therapeutic effect of the antacid. In the fed state, the Tmax for FCT and FACT are relatively the same, 2.9 hours. The mean intragastric pH for FACT and FCT are similar to each other during the 5-9 hour post-dose period. During the first 60 minutes post-dose, the intra-esophogeal and intra-gastric pH are higher for FACT and antacid than for FCT and placebo. Since the 35 minute difference of FACT and FCT Tmax occurs between the 1-3 hour time points, after the therapeutic benefit of co-administered antacid has passed, the Clinical Pharmacology and Biopharmceutics Reviewer expressed concern that this could lead to patients re-dosing prior to the original Famotidine dose reaching Tmax. In the pattern of use study, many patients second dosed within the first, second and third hours after taking the original dose of medication. Because there is no similar dosing table for NDA 20-325, famotidine 10mg tablets, a comparison of this aspect of the dosing habits cannot be made. Therefore, it is not clear whether the second dosing within the first three hours is occurring as a result of the pharmacokinetic profile of the drug or unrelated. One hundred eleven of the 139 patients who took more than one dose/day at least once separated the doses by greater than 3 hours.

Seventy-six percent of the patients in the study were considered to be compliant. This number, as it stands, is less than desirable, especially considering that the study group patients had a higher reading level than the general population. The study defines noncompliance very narrowly as those who took more than one pill at one dose or more than two pills per day. This definition does not capture, those who took more than two pills within 24 hours but no more than two pills within each day. Review of the line list shows that approximately 14% of the volunteers took more than 2 pills within a 24-hour period at least once, and often on many occasions. This extra dosing was evident if one looked at the dosing from one day to the next but within a 24-hour time interval.

The sponsor should also have assessed compliance in terms of indication used. Since this information was not obtained, no additional information is available on this issue. Excluding the 88 "lost to follow-up" patients could have resulted in bias since it is possible that lost to follow-up patients could have had a high noncompliance rate. However, for the safety analysis it was assumed that the 88 patients did take study medication. Thus there is a clear inconsistency in handling missing data.

One ingredient in the chewable tablet is _____ Peppermint is known to decrease the lower esophageal sphincter pressure. I wonder if this flavoring contributed to increased symptoms among those people who used more than the recommended two tablets during a 24-hour period.

4. Safety Issues:

The underreporting of side effects in the FACT study is likely for several reasons. There was no space allocated on the diary cards for patients to report side effects. In the Use Study for Famotidine 10mg (NDA 20-325) the diary designated places for patients to record both their reasons for taking the study medication, and any adverse effects, especially those signs and symptoms that they might have found inconvenient to report by telephone. In that study, 30% of patients reported one or more adverse effect. In this use study, a patient had to make a phone call to report adverse effects. Only 9 people (1.9%) did so. Additionally, FACT combines two drugs already available OTC; this may have also contributed to the likely underreporting of side effects.

The FACT safety analysis included 465 volunteers, of whom 88 individuals in the safety population were "lost to follow-up." In the definition of the safety analysis population, the study did not specify when and how to handle the missing data from the 88 patients. The assumption in the safety analysis, that the 88 did not experience any adverse events, artificially enlarges the denominator of the safety analysis, maybe erroneously yielding a small adverse event rate. Even if these 88 individuals were subtracted from the 465 total, the FACT safety study might logically expect to see more patients reporting side effects.

5. Summary:

This actual usage study looks at a medication that combines an antacid and acid-reducer that are already sold OTC individually. The 76.1% compliance rate is lower than desirable considering the reading level of the study population. When one considers the other compliance issues mentioned above, there are concerns about the actual compliance rate of the study. These should be addressed before FACT should be available OTC. Further, the labeling, as it currently exists, should be expanded to include warnings about renal disease, adverse reactions to H2 blockers and other drug interactions as mentioned above, as well as a warning not to take concurrently with other famotodine products (OTC or prescription).

/S/

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/S/

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1/13/99

NDA 20-958 Pepcid AC Advanced Acid Reducer/Antacid tablets.

MEDICAL OFFICER REVIEW
Division of Over-the-Counter Drug Products
Date: 11/30/98
Medical Officer: Andrea Leonard-Segal, MD

CC:
Original NDA 20-958
HFD-180 LTalarico/KRobie-Suh/MFolkendt
HFD-560 DBowen/LKatz/ASegal/RNeuner/HCothran/GChang/MLessing/ARothschild
HFD-560 Div. File
HFD-725 QLi/Slin