CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958

MEDICAL REVIEW

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA:	19-462; 19-510; 19-527; 20-249; 20-752; 20-958
Sponsor:	Merck & Co. West Point, PA 19486-0004
Drug name:	Pepcid (famotidine) Tablets; Injection; Oral suspension; Injection Premix; RPD™; Complete Tablets
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Table of Abbreviations:

Abbreviation	Term
AE	Adverse experience
AUC	Area under the curve
C_{max}	Maximum plasma concentration
Cl	Clearance
GERD	Gastroesophageal reflux disease
I.V.	Intravenous
NOS	Not otherwise specified
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	Per oral
T_{max}	Time to maximum plasma concentration
V_d	Apparent volume of distribution

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EXECUTIVE SUMMARY

I. Recommendations:

In response to a Written Request for Pediatric Studies and in order to provide labeling information on the use of famotidine in pediatric patients less than 1 year of age and obtain pediatric exclusivity (as per FDAMA), the sponsor has performed and submitted three pediatric studies. These studies involved pediatric patients less than 1 year of age who had symptoms of gastroesophageal reflux disease (e.g., vomiting (spitting up), irritability (fussing)). The studies include: a randomized, treatment withdrawal, clinical outcomes and safety study in pediatric patients less than 1 year of age (Study 131); a pharmacokinetic study in pediatric patients up to 1 year of age (Study 129); and a pharmacokinetic/pharmacodynamic study of intravenous famotidine in pediatric patients less than 1 month of age (Study 136). Also, a relative bioavailability study of oral tablet compared to oral suspension formulation in adults is submitted (Study 130). A total of 71 patients, 12 of whom were less than 1 month of age, were enrolled in these studies.

Based on the information provided in these studies, this application is approvable. The proposed labeling should be modified as follows:

1. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS,** as recommended by FDA Clinical Pharmacology and Biopharmaceutics, delete the sentence: "In another clinical study of the 5 pediatric patients evaluated for pharmacodynamics, 2 patients 0-3 months of age with a gastric pH <4 at baseline had gastric pH increase to greater than 4 for 11 and 26.5 hours after famotidine doses of 0.25 and 0.5 mg/kg, respectively."

2. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS,** delete the new sub-section titled: Clinical Studies – Gastroesophageal Reflux Disease (GERD).

3. Under **PRECAUTIONS**, in the new sub-section: Pediatric patients <1 year of age, delete the second paragraph and replace it with the following:

   "In a double-blinded, randomized, treatment-withdrawal study 35 pediatric patients <1 year of age who were diagnosed as having gastroesophageal reflux disease were treated for up to 4 weeks with famotidine oral suspension (0.5 mg/kg/dose or 1 mg/kg/dose). Also, caregivers were instructed to provide conservative treatment including thickened feedings. The famotidine dosing regimen was once daily for patients <3 months of age and twice daily for patients ≥3 months of age. *After 4 weeks of treatment patients were randomly withdrawn from the treatment and followed an additional 4 weeks for adverse events and symptomatology. Patients were evaluated for vomiting (spitting up), irritability (fussiness) and global assessments of improvement. Enrolled patients were diagnosed primarily by history of vomiting (spitting up) and irritability (fussiness). The study patients ranged in age at entry from 1.3 to 10.5 months (mean 5.6±2.9 months), 57% were female, 91% were white and 6% were black. Most patients (27/35) continued into the treatment withdrawal phase of the study. Two patients discontinued famotidine due to adverse events. Most patients improved during the initial treatment phase of the study. Results of the treatment withdrawal phase were difficult to interpret because of small numbers of patients. Of the 35 patients enrolled in the study, agitation was observed in 5 patients on famotidine that resolved when the*

medication was discontinued; agitation was not observed in patients on placebo (see ADVERSE REACTIONS, Pediatric Patients."

4. Under **PRECAUTIONS**, in the new sub-section: Pediatric patients <1 year of age, add as a new paragraph at the beginning of the sub-section the following: Use of PEPCID in pediatric patients <1 year of age is supported by evidence from adequate and well-controlled studies of PEPCID in adults, and by the following studies in pediatric patients <1 year of age."

5. Under **PRECAUTIONS**, in the new sub-section: Pediatric patients <1 year of age, in the last paragraph, revise the second part of the first sentence to read: "the safety and benefit of famotidine treatment beyond 4 weeks have not been established."

6. Under **DOSAGE AND ADMINISTRATION**, new section Dosage for Pediatric patients <1 year of age, Gastroesophageal Reflux Disease (GERD), delete the entire paragraph and replace it with the following:

"Dosage for Pediatric Patients <1 year of age
Gastroesophageal Reflux Disease (GERD. See **PRECAUTIONS**, Pediatric patients <1 year of age. The studies described in **PRECAUTIONS**, Pediatric Patients <1 year of age suggest the following starting doses in pediatric patients <1 year of age:
Gastroesophageal Reflux Disease (GERD) - 0.5 mg/kg/dose of famotidine oral suspension for the treatment of GERD for up to 8 weeks once daily in patients <3 months of age and 0.5 mg/kg/dose twice daily in patients 3 months to <1 year of age. Patients should also be receiving conservative measures (e.g., thickened feedings)."

7. Under **ADVERSE REACTIONS**, in the new Pediatric Patients sub-section, revise the section as follows: "Pediatric Patients. In a clinical study in 35 pediatric patients <1 year of age with GERD symptoms (e.g., vomiting (spitting up), irritability (fussing)), agitation was observed in 5 patients on famotidine that resolved when the medication was discontinued."

8. *Under the **DOSAGE AND ADMINISTRATION** section, include information regarding the use of the parenteral products in pediatric patients <1 year of age.*

B. Summary of Clinical Findings:

Study 131 was a multicenter, randomized, double-blind, placebo-controlled study with a withdrawal design. Pediatric patients less than 12 months of age with a clinical diagnosis of geastroesophageal reflux disease (diagnosis mostly based on vomiting (spitting up) and irritability (fussing) were enrolled. During an initial single-blind phase, patients were randomized to receive famotidine oral suspension once daily dose of either 0.5mg/kg/dose [0.25mg/kg/dose I.V. injection, as alternate] or 1.0 mg/kg/dose [0.5mg/kg/dose I.V. injection, as alternate]. Patients 3 months and older received famotidine twice daily dose of either 0.5mg/kg/dose [0.25mg/kg/dose I.V. injection, as alternate] or 1.0 mg/kg/dose [0.5mg/kg/dose I.V. injection, as alternate]. Treatment was continued for up to 4 weeks after which paitients were randomized in a Double-Blind phase to continued famotidine or placebo for an additional 4 weeks. Clinical outcome measures evaluated included vomiting (spitting up), irritability (fussing), apnea episodes, and caretaker and physical global assessments of improvement. Adverse

experiences were recorded. A total of 35 patients were enrolled. Of these 26 continued into the double-blind phase. Numbers of patients were too small to make any conclusions as to efficacy. Most patients improved over the course of the study. Patients generally tolerated famotidine well. There were two study withdrawals due to adverse events. Agitation was observed in 5 of 35 patients.

In Study 129 pharmacokinetics of famotidine were evaluated in infants up to 1 year of age and In Study 136 pharmacokinetic and pharmacodynamic parameters of famotidine were evaluated in 10 pediatric patients <1 month of age. Plasma clearance was reduced and elimination half-life was prolonged in pediatric patients <3 months of age compared to older pediatric patients. Pharmacokinetic values in pediatric patients older than 3 months were comparable to those in adults. Clearance was 0.13L/kg/hr, 0.21L/kg/hr and 0.49L/kg/hr in pediatric patients <1 month of age, <3 months of age, and >3 to 12 months of age, respectively. Elimination half-life was 10.5 hrs, 8.1 hrs, and 4.5 hrs in pediatric patients <1 month of age, <3 months of age, and >3 to 12 months of age, respectively.

In Study 130, a relative bioavailability study of famotidine tablets compared to famotidine oral suspension, the sponsor found bioavailability of the two formulations to be comparable.

The pediatric studies in this submission were conducted according to the Written Request for Pediatric Studies and pediatric exclusivity has been granted.

CLINICAL REVIEW

Background and Rationale:

Pepcid (famotidine) is a histamine H_2-receptor antagonist approved for use in adult patients for short term treatment of active duodenal ulcer, maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer; short term treatment of active benign gastric ulcer, short term treatment of gastroesophageal reflux disease (GERD), and treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas). Pepcid also is labeled for use in pediatric patients 1 to16 years of age for peptic ulcer disease and GERD with or without esophagitis including erosions and ulcerations. This use is supported by adequate and well-controlled studies of Pepcid in adults and by pharmacokinetic/pharmacodynamic (PK/PD) studies in pediatric patients 1-15 years of age.

On December 20, 1999 the Agency issued a Pediatric Request for studies of famotidine in pediatric patients aged 0 to1 year of age. In this submission the sponsor has provided a Pediatric Supplement including a pharmacokinetic and pharmacodynamic study of famotidine in neonates and infants and a clinical outcome and safety study of famotidine in neonates and infants.

Materials Submitted and Reviewed:

The application is submitted entirely in electronic format.

The main clinical data provided consists of four clinical studies as follows:

- Protocol 131 (a placebo-controlled safety and clinical outcomes study in infants up to 1 year);
- Protocol 129 (a PK study in infants up to 1 year);
- Protocol 130 (a relative bioavailability study of famotidine suspension vs. Pepcid tablets in healthy adults);

- Protocol 136 (a PK/PD study in neonates [age<1month]).

No investigators/subinvestigators in these studies held a financial interest that required disclosure. One investigator and one subinvestigator in Study 131 and one in Study 129 did not return the disclosure forms. One sub-investigator in Study 129 was no longer at the site.

The sponsor also has provided published clinical literature and summary of safety information.

Clinical Studies:

I. **Protocol 131: Multicenter Study: A Randomized Placebo-Controlled Evaluation of Oral or I.V. Famotidine in the Treatment of Infants with Gastroesophagel Reflux Disease (GERD)**

This was a multicenter, randomized, double-blind, placebo-controlled study designed to be conducted in at least 30 patients age 0-12 months having a clinical diagnosis of GERD. This study was carried out from 1/27/2000 through 6/14/2000 at 3 U.S. sites.

A. **Objectives:** The primary objective was to evaluate the safety and tolerability of famotidine administered up to 8 weeks. The secondary (exploratory objective) was to evaluate the clinical effects of famotidine when given for up to 8 weeks to alleviate GERD symptoms (crying or fussing, spitting up), and global assessments of GERD (by parents/caregivers and by physician), and growth parameters (height, weight, head circumference).

B. **Study design:** This was a multicenter (3 centers), double-blind, placebo-controlled randomized withdrawal study consisting of an Observer-Blind Phase and a Double-Blind Phase. For the Observer-Blind Phase patients were randomly allocated to receive famotidine Regimen A (lower dose) or B (higher dose) for Weeks 1 through 4. During Weeks 5 to 8 (Double-Blind Phase) patients were randomly assigned either to continue famotidine treatment at same dose or to receive placebo instead of famotidine. Evaluations of clinical endpoints were made at Weeks 2, 4, 6 and 8 (end of treatment).

At Week 2 patients at the lower dosage level who were unable to continue treatment because of lack of efficacy were offered opportunity to continue at the higher dosage level (dose escalation). For randomization into the Double-Blind Phase these patients were randomized according to their original famotidine dose assignment.

C. **Subjects:** These were to be about 30 male or female patients aged 0 to 12 months at enrollment having an established diagnosis of GERD and requiring treatment for at least 8 weeks. Excluded were patients with: history of respiratory complication of GERD; apparent life-threatening event; unstable renal, cardiovascular, or hepatic disease or diabetes; coexisting cancer; history of illness that might confound interpretation of study results or put patient at additional risk; patient unable to discontinue prior proton pump inhibitor, prokinetic agent, H2 receptor antagonist or antacid; known hypersensitivity to famotidine or other H2 receptor antagonist; inability to comply with the protocol.

D. **Study drug:** During the Observer-Blind Phase: Patients <3 months of age were to receive investigational famotidine oral suspension (8/mg/ml) once daily dose of either 0.5mg/kg/dose [0.25mg/kg/dose I.V. injection, as alternate] (Regimen A) or 1.0

mg/kg/dose [0.5mg/kg/dose I.V. injection, as alternate] (Regimen B). Patients ≥3 months of age were to receive investigational famotidine oral suspension twice daily dose of either 0.5mg/kg/dose [0.25mg/kg/dose I.V. injection, as alternate] (Regimen A) or 1.0 mg/kg/dose [0.5mg/kg/dose I.V. injection, as alternate] (Regimen B). During the Double-Blind Phase patients completing the first phase of the study were to be re-randomized to receive either continued same dose of famotidine or placebo. Near the end of study enrollment, the protocol was amended to use the marketed Famotidine Oral Suspension (8mg/ml) instead of the investigational famotidine suspension for this part of the study.

The investigational oral formulation was prepared by first preparing the Pepcid Oral Suspension as labeled to give a solution of 8mg/ml. Then the solution was diluted to give 1mg/ml using OraSweet^{R}. (See Appendix for description of preparation of formulations). Chemistry portion of the application indicates that sponsor discovered approximately 3.5 months into the study formation of a previously unrecognized degradate) when famotidine suspension was prepared using OraSweet^{R}. (See FDA Chemistry, Manufacturing and Controls Review for further discussion).

E. Study plan: The schedule of study procedures is shown in the sponsor's table below.

Schedule of Clinical Observations and Laboratory Measurements

	Treatment Weeks								
Clinic Visit I.D.:	Beginning of Baseline Week 0[1]	Phone Contact Week 1	Observer-Blind Week 2	Phone Contact Week 3	Randomization Visit, Beginning of Double-Blind Phase End of Week 4[2]	Phone Contact Week 5	Double-Blind Follow-Up Week 6	Phone Contact Week 7	End of Double-Blind Week 8
Informed consent	X								
Medical history	X								
Vital signs (weight, length, head circumference)	X		X		X		X		X
Laboratory: CBC, creatinine, AST, ALT, GGT	X								X
Telephone contact		X		X		X		X	
Dispense symptom diary	X		X		X		X		
Collect symptom diary			X		X		X		X
Adverse experience assessment			X		X		X		X
GERD symptom questionnaire	X								
GERD symptom assessments[3]			X		X		X		X
Dispense medication and medication diary	X		X		X		X		
Collect and review medication diary			X		X		X		X

[1] Optional phone contact may have preceded; Days -3 to -10.
[2] With the implementation of Protocol Amendment 131-04, all participating patients were switched to marketed famotidine oral suspension. This included patients who would have been randomized to placebo treatment at Week 4. The Study Pharmacist and Study Drug Coordinator were not blinded to treatment assignment; the clinical coordinator and investigator remained blinded to treatment assignment.
[3] Includes irritability, growth, and global assessments.

Data Source: [3.2.1; 3.2.5]

At the baseline visit informed consent was obtained, a diagnostic questionnaire was completed and history and physical examination were performed. Qualified patients were randomized into Observer-Blind Phase. At Weeks 2 and 4 GERD symptom assessments (including irritability, growth and parent/caretaker and physician global assessments) were made. For weeks that patients were not seen in clinic, telephone contact was made. At end of treatment patients underwent a brief physical examination, the medication record was reviewed, and the symptom diary was reviewed. Final

assessments were made and blood was taken for clinical laboratory studies. Patients discontinuing prior to 8 weeks were to have end of study procedures and assessments done at time of discontinuation.

F. **Efficacy parameters:** Assessments were made according to the following:

Assessments of Irritability (at each followup visit: Weeks 2, 4, 6 and 8):

1. Crying or fussing – "Considering the past 2 weeks, how many hours does the baby cry or fuss each day?"
   - Less than 10 minutes
   - 10 minutes to an hour
   - one hour to 3 hours
   - more than 3 hours

2. Spitting up – "Considering the past 2 weeks, how often does the baby usually spit up?"
   - Less than once a day
   - One to 3 times a day
   - Three to 5 times a day
   - More than 5 times a day

3. Spitting up - "Considering the past 2 weeks, how much does the baby usually spit up?"
   - A teaspoonful or less
   - A teaspoonful to a tablespoonful
   - A tablespoonful to an ounce
   - An ounce or more, but less than the whole feeding
   - The whole feeding

Global Assessments (at each followup visit: Weeks 2, 4, 6 and 8:

1. Parent global assessment – Parent/caregiver responded to question: "Since your last visit, do you feel that your baby is:
   - Completely well
   - Somewhat improved
   - Not at all improved
   - Worse

2. Physician global assessment - "Since the last visit, do you feel that the baby is:
   - Completely well
   - Somewhat improved
   - Not at all improved
   - Worse

Assessments of Growth (at each visit: Weeks 0, 2, 4, 6 and 8):

1. Weight
2. Length
3. Head circumference

G. **Safety:** Occurrence of adverse events was evaluated at each visit. Events were rated as to intensity, seriousness, duration, action taken and possible relationship to study drug. Adverse events were to be collected to 14 days after conclusion of last Double-Blind treatment visit. Clinical laboratory studies were conducted. Renal function was determined by serial creatinine measurements and calculation of creatinine clearance.

H. **Statistical methods:** For safety and efficacy evaluations the primary statistical approach was estimations, including percentages, incidences and corresponding 95% confidence intervals. The study was not statistically sized or powered to detect a prespecified treatment difference. Primary analyses were intent-to-treat (population not specifically defined); all tests were 2-sided at a significance level of 5%. The primary comparison was of the incidences of adverse experiences occurring during the study (at

8 Weeks). Treatment comparisons were made with regard to incidence of: (1)at least one AE, (2)a specific AE; (3)a drug-related AE; (4)a serious AE; and (5)discontinuation due to an AE.

For efficacy analyses treatment comparisons were made between famotidine doses versus their placebo. Within group comparisons also were made. Irritability was compared using Wilcoxon rank sum test on week specific categorical assessment. Within-group comparisons were made using Wilcoxon's signed rank test. Assessments of growth were summarized at visit weeks and between-treatment comparisons were made using Wilcoxon-Mann-Whjtney test and within-group comparison was made using Wilcoxon's signed rank test. For comparison of global assessments between groups Wilcoxon rank sum test was used and for within group comparisons Wilcoxon's signed rank test was used. For infants discontinuing during the trial, efficacy assessment obtained at time of discontinuation was to be carried forward to subsequent weeks. All efficacy analyses were exploratory in nature. No adjustments for multiplicity were made.

I. **Compliance:** Compliance was assessed by review of patient medication diaries.

J. **Amendments:** The study had four amendments, two of which occurred after enrollment into the study had begun. Amendment 3, issued on the date enrollment into the study began, defined "complete the study" as undergoing treatment for at least 2 weeks, or discontinuing due to an adverse experience or lack of efficacy and modified the entry criteria to exclude patients <32 weeks gestational age. Amendment 4, issued about 3 months after initiation of patient enrollment, discontinued treatment with the investigational oral famotidine formulation (1mg/ml) and matching placebo, because of degradate formation. The investigational famotidine formulation was replaced with marketed famotidine suspension.

K. **Results:**

1. Enrollment and Demographics: Three study sites enrolled a total of 35 patients (Czinn, 4 patients; Liacouras, 6 patients; Orenstein, 25 patients).

   Demographic and baseline characteristics of the study population are summarized in the sponsor's table below:

Baseline Patient Characteristics by Treatment Group

	Fam 0.5 mg (N=18)*		Fam 1.0 mg (N=17)*		Total (N=35)	
	n	(%)	n	(%)	n	(%)
Gender						
Male	7	(38.9)	8	(47.1)	15	(42.9)
Female	11	(61.1)	9	(52.9)	20	(57.1)
Race						
White	17	(94.4)	15	(88.2)	32	(91.4)
Black	1	(5.6)	1	(5.9)	2	(5.7)
Bi-Racial	0	(0.0)	1	(5.9)	1	(2.9)
Age (Months)						
0 to 3‡	3	(16.7)	5	(29.4)	8	(22.9)
3 to 12	15	(83.3)	12	(70.6)	27	(77.1)
>12	0	(0.0)	0	(0.0)	0	(0.0)
Mean	5.8		5.4		5.6	
SD	2.8		3.2		2.9	
Median	5.4		5.3		5.3	
Range	1.6 to 10.2		1.3 to 10.5		1.3 to 10.5	
Weight (kg)						
Mean	7.0		6.9		7.0	
SD	1.4		2.4		1.9	
Median	6.9		6.5		6.6	
Range	4.8 to 9.8		3.4 to 11.7		3.4 to 11.7	
Height (cm)						
Mean	64.9		62.8		64.0	
SD	6.2		10.8		8.6	
Median	65.9		63.6		65.8	
Range	54.5 to 75		35 to 74.8		35 to 75	
Head Circumference (cm)						
Mean	42.1		42.3		42.2	
SD	2.8		4.0		3.4	
Median	42.8		42.5		42.8	
Range						
Crying or Fussing						
<10 Min	5	(27.8)	1	(5.9)	6	(17.1)
10 Min to 1 hr/day	4	(22.2)	3	(17.6)	7	(20.0)
1 to 3 hrs/day	5	(27.8)	7	(41.2)	12	(34.3)
>3 hrs/day	4	(22.2)	5	(29.4)	9	(25.7)
Spitting Up Frequency						
<1x/Day	1	(5.6)	1	(5.9)	2	(5.7)
1 to 3x/Day	4	(22.2)	3	(17.6)	7	(20.0)
3 to 5x/Day	3	(16.7)	5	(29.4)	8	(22.9)
>5x/Day	10	(55.6)	8	(47.1)	18	(51.4)
Spitting Up Amount						
≤1 Tsp	2	(11.1)	0	(0.0)	2	(5.7)
1 Tsp to 1 tbsp	3	(16.7)	5	(29.4)	8	(22.9)
1 Tbsp to 1 ounce	6	(33.3)	3	(17.6)	9	(25.7)
≥1 Ounce	7	(38.9)	8	(47.1)	15	(42.9)
Whole feeding	0	(0.0)	1	(5.9)	1	(2.9)

n (%) Number (percent) of patients in each category.
* All patients are displayed as initially randomized, including those who underwent dose escalation.
‡ No patient was <1 month of age at enrollment.

Data Source: [4.3; 4.6; 4.7]

Sponsor's table, Table 9 from study report

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Generally the baseline characteristics of patients randomized to the two initial famotidine treatment groups were similar. Possibly the time spent crying or fussing and the amount of spitting up was somewhat more in the patients randomized to famotidine 1.0mg. Infants ranged in age at entry from 1.3 to 10.5 months (mean 5.6 months; median 5.3 months). About 57% were female.

By and large the diagnosis of GERD in these patients was made based on clinical history of vomiting (spitting up) and irritability (fussiness). Some infants had also history of occasional projectile vomiting and some also had history of "noisy breathing". Only 1 patient was listed as having endoscopy during study (which showed erythema, otherwise normal). Narratives mentioned endoscopy for 2 other pateints but no results were available. Few patients had history of apneic episodes. GERD symptoms were mild in most cases. Most infants had been on some therapy within the 30 days prior to entering the study (61% of famotidine 0.5mg patients; 82% of famotidine 1.0mg patients). More famotidine 0.5mg patients had been on cisapride prior to study than had famotidine 1.0mg patients.

2. Disposition of Patients: Disposition of patients is summarized in the following table:

Disposition of Patients

	Number of Patients				
Observer-Blind Phase:					
					Total
Study Drug	Famotidine 0.5mg		Famotidine 1.0mg		
Patients treated[a]	18		17		35
Completed the study[b]	18		16		34
Completed the phase	14		13		27
Discontinued during the phase: Clinical adverse event Withdrew consent	4 2 2		4 4 0		8 6 2
Continued to double-blind phase	14		13		27
Double-Blind Phase:					
					Total
Double-Blind Phase	Placebo	Famotidine 0.5mg	Placebo	Famotidine 1.0mg	
Patients treated	5	8[c]	6	7	26
Completed the phase	1	2	3	2	8
Switched to marketed formulation	2	2	1	3	8
Discontinued during the phase: Clinical adverse experience Lost to follow-up Therapy ineffective	2 0 1 1	4 1 0 3	2 0 0 2	2 0 0 2	10 1 1 8

[a] All patients are displayed as initially randomized, including those who underwent dose escalation. Three patients assigned to famotidine 0.5mg/kg dose underwent dose escalation.

[b] Defined as undergoing treatment for at least 2 weeks, or discontinuing due to an adverse experience or lack of efficacy

[c] One patient was assigned to the double-blind famotidine 0.5mg group but did not receive study medication (pt was treated with open label marketed famotidine oral suspension).

reviewer's table based on sponsor's Tables 14 and 15

For Observer-Blind Phase this table includes patients who underwent dose escalation. Display shows initial randomization.

The sponsor's diagram below shows patient disposition and reasons for discontinuation for individual patients.

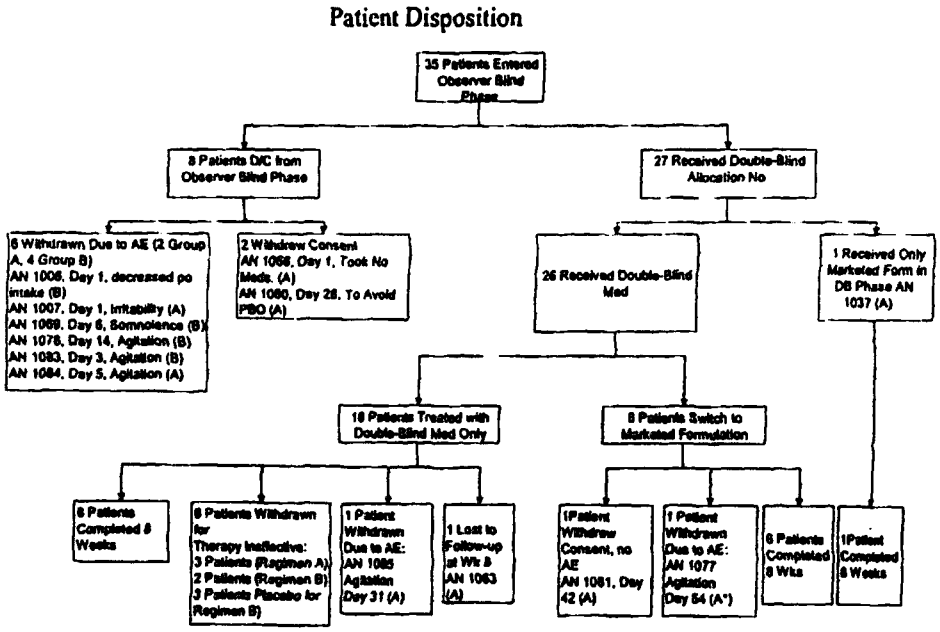

Figure 5—This figure summarizes patient discontinuation. Patients withdrawn due to adverse experiences of agitation, somnolence, or ineffective therapy (lack of efficacy) are identified by allocation number. The regimen being taken at the time of discontinuation is also noted: A=famotidine-0.5 mg/kg/dose; A*=famotidine-0.5 mg/kg/dose, escalated to famotidine 1.0 mg/kg/dose at Week 2; B=famotidine 1.0 mg/kg/dose.
Data Source: [4.5; 4.8]

Sponsor's diagram

3. Efficacy Analysis: All efficacy analyses were exploratory only. Results for the Observer-Blind and Double-Blind Phases are summarized in the following table:

Changes in Efficacy Parameters during Observer-Blind Phase and Double-Blind Phase

	Number of Patients															
	Observer-Blind Phase:															
	Famotidine 0.5 mg (N=18)								Famotidine 1.0mg (N=17)							
	Improved	Same	Worse	Missing	Improved	Same	Worse	Missing	Improved	Same	Worse	Missing	Improved	Same	Worse	Missing
Week 2:																
Crying or Fussing	6	7	3	2					9	5	1	2				
Spitting up- Frequency	8	7	1	2					13	2	1	1				
Spitting up-Quantity	10	4	2	2					11	4	1	1				
Parent global[a]	14	2	0	2					15	0	1	1				
Physician global[a]	14	1	0	3					15	0	0	2				
Week 4:																
Crying or Fussing	5	9	1	3					8	3	1	5				
Spitting up- Frequency	8	5	2	3					9	4	0	4				
Spitting up-Quantity	8	5	2	3					9	3	1	4				
Parent global[a]	10	3	2	3					11	2	0	4				
Physician global[a]	10	4	1	3					12	1	0	4				
	Double-Blind Phase:															
	Placebo (N=5)				Famotidine 0.5mg (N=8)				Placebo (N=6)				Famotidine 1.0 mg (N=7)			
Week 6:																
Crying or Fussing	2	1	2	0	0	4	4	0	2	2	2	0	0	3	3	0
Spitting up- Frequency	1	2	2	0	1	5	2	0	3	0	3	0	1	1	4	0
Spitting up-Quantity	2	1	2	0	1	6	1	0	1	3	2	0	3	2	1	0
Parent global[a]	3	1	1	0	4	1	3	0	4	0	2	0	3	1	2	0
Physician global[a]	2	1	1	1	3	2	2	1	3	0	3	0	3	1	2	0
Week 8:																
Crying or Fussing	0	0	1	4	0	1	1	6	2	0	1	3	0	2	1	3
Spitting up- Frequency	0	1	0	4	0	2	0	6	1	1	1	3	1	0	2	3
Spitting up-Quantity	0	0	1	4	0	1	1	6	1	2	0	3	2	1	0	3
Parent global[a]	0	1	0	4	0	2	0	6	2	0	1	3	1	1	1	3
Physician global[a]	0	1	0	4	2	0	0	6	2	0	1	3	1	2	0	3

[a] Improved= "Completely well" or "Somewhat improved"; Same = "not at all improved"

reviewer's table, based on sponsor's Tables 14, 15, 18, 20, 22, 25, 27, 29, 31, 33 and 34.

During the 4-week Observer-Blind Phase the number and percentages of patients improving with regard to the various efficacy parameters were similar between the famotidine 0.5mg group and the famotidine 1.0mg group. There were no significant differences in changes from baseline between groups for any of these parameters. However, numbers of patients are small and some patients did not have efficacy assessments available for some endpoints.

During the Double-blind Treatment period there was no apparent difference between treatment groups in numbers of patients improving or worsening. Numbers of patients in this phase of the study were very small and some of those patients in each treatment group did not have evaluations available for all endpoints.

After completion of the the Double-blind Phase of the study, 9 patients continued treatment with open-label marketed Famotidine Oral Suspension. At week 8 by physician global assessment and spitting up quantity all 9 of these patients had improved. The majority also had improved with regard to crying and fussing, spitting up frequency and parent assessment. None had worsened.

Changes in growth measurements during the study are summarized in the following two sponsor's tables:

Table 23

Summary of Growth Measurements and Changes From Baseline
by Week and Treatment
Observer-Blind Phase

		Fam 0.5 mg (N=16)†			Fam 1.0 mg (N=16)†		
	Week	N_1	Measure Mean (std)	Change Mean (std)	N_1	Measure Mean (std)	Change Mean (std)
Weight (kg)	0	15	7.1 (1.2)	-	15	7.0 (2.5)	-
	2	15	7.4 (1.2)	0.3 (0.2)	15	7.3 (2.5)	0.3 (0.2)
	4	15	7.6 (1.2)	0.5 (0.3)	13	7.5 (2.6)	0.6 (0.3)
Length (cm)	0	15	65.3 (5.6)	-	15	63.2 (11.1)	-
	2	15	66.4 (5.1)	1.1 (1.3)	15	64.0 (10.9)	0.9 (1.2)
	4	15	67.1 (4.4)	1.8 (1.7)	13	64.7 (11.2)	2.1 (1.6)
Circumf (cm)	0	15	42.1 (2.7)	-	14	42.4 (4.2)	-
	2	13	42.1 (2.8)	0.3 (0.5)	15	42.3 (4.2)	0.2 (1.1)
	4	13	43.1 (2.1)	0.7 (0.5)	13	42.8 (4.2)	0.7 (1.4)

No significant difference was found between groups.
N=Number of patients in the observer-blind efficacy analysis per treatment group.
N_1 Number of patients with non-missing evaluation.
† All patients are displayed as initially randomized, including those who underwent dose escalation.

Data Source: [4.6]

Table 32

Summary of Growth Measurements and Changes From Week 4
by Week and Treatment
Double-Blind Phase

		Fam 0.5 mg/Fam 0.5 mg (N=8)†			Fam 0.5 mg/Placebo (N=5)†			Fam 1.0 mg/Fam 1.0 mg (N=6)†			Fam 1.0 mg/Placebo (N=6)†		
	Week	N_i	Measure Mean (std)	Change Mean (std)	N_i	Measure Mean (std)	Change Mean (std)	N_i	Measure Mean (std)	Change Mean (std)	N_i	Measure Mean (std)	Change Mean (std)
Weight (kg)	6	8	8.0 (1.4)	0.2 (0.3)	5	7.1 (0.8)	0.2 (0.2)	6	7.2 (2.8)	0.2 (0.2)	6	8.6 (2.2)	0.0 (0.2)
	8	2	7.7 (1.6)	0.3 (0.0)	1	7.5 (-)	0.1 (-)	3	7.1 (1.3)	0.4 (0.2)	3	8.3 (2.8)	0.5 (0.3)
Length (cm)	6	8	68.8 (4.4)	1.1 (1.3)	4	68.5 (3.5)	1.1 (0.9)	6	61.4 (12.4)	0.6 (16.2)	6	70.4 (5.6)	0.3 (1.2)
	8	2	67.0 (7.1)	1.0 (1.4)	1	71.0 (-)	1.0 (-)	3	56.5 (14.5)	-7.6 (16.7)	3	68.2 (6.8)	0.7 (1.5)
Circumf (cm)	6	8	43.9 (1.8)	0.4 (0.4)	4	43.8 (2.1)	0.2 (0.4)	6	42.9 (4.7)	0.3 (0.8)	6	44.0 (3.8)	0.2 (0.9)
	8	2	43.7 (1.9)	1.4 (0.6)	1	46.5 (-)	0.5 (-)	3	44.0 (3.0)	2.0 (1.3)	3	42.7 (4.4)	0.7 (1.2)

N = Number of patients in the Double-Blind Phase efficacy analysis per treatment group.
N_i = Number of patients with non-missing evaluation.
† All patients are displayed as initially randomized, including those who underwent dose escalation.

Data Source: [4.6]

Mean weight, length and head circumference appeared to increase slightly in both treatment groups over the course of Observer-Blind Phase. For the Double-Blind Phase the number of patients is too small to allow any meaningful comparison of treatment groups.

4. Safety Analysis: Most patients (30 of 35) experienced one or more adverse events during the course of the study. A larger percentage of participating patients experienced adverse events during the Baseline Phase of the Study than during the Double-Blind Phase. The sponsor's table below shows the adverse events that occurred during the study:

Table 39

Number (%) of Patients With Specific Clinical Adverse Experiences (Incidence ≥0% in 1 or More Treatment Groups) by Body System All Study Phases

	Fam 0.5 mg (N=18)[1]			Fam 1.0 mg (N=17)[1]		
	n	(%)	DR	n	(%)	DR
Patients with one or more adverse experiences (AEs)	13	(72.2)	4	17	(100.0)*	7
Patients with no AEs	5	(27.8)		0	(0.0)	
Body as a Whole/Site Unspecified	1	(5.6)		3	(17.6)	
Fever	0	(0.0)		3	(17.6)	
Infection, fungal	1	(5.6)		0	(0.0)	
Digestive System	5	(27.8)	1	5	(29.4)	2
Anorexia	1	(5.6)	1	1	(5.9)	1
Candidiasis, oral	0	(0.0)		1	(5.9)	1
Constipation	1	(5.6)		2	(11.8)	
Diarrhea	1	(5.6)		1	(5.9)	
Gastroenteritis	1	(5.6)		0	(0.0)	
Hematemesis	1	(5.6)		0	(0.0)	
Vomiting	1	(5.6)	1	1	(5.9)	
Hemic & Lymphatic System	0	(0.0)		1	(5.9)	
Lymphadenopathy	0	(0.0)		1	(5.9)	
Nervous System & Psychiatric	7	(38.9)	4	7	(41.2)	6
Agitation	3	(16.7)	3	2	(11.8)	2
Falling	1	(5.6)		0	(0.0)	
Headache	1	(5.6)	1	1	(5.9)	1
Irritability	3	(16.7)	1	1	(5.9)	
Somnolence	0	(0.0)		3	(17.6)	3
Respiratory System	7	(38.9)		7	(41.2)	1
Congestion, respiratory	0	(0.0)		1	(5.9)	
Cough	0	(0.0)		1	(5.9)	
Discomfort, pharyngeal	1	(5.6)		0	(0.0)	
Dyspnea	0	(0.0)		1	(5.9)	
Hiccups	0	(0.0)		1	(5.9)	1
Infection, respiratory	1	(5.6)		1	(5.9)	
Infection, respiratory, upper	2	(11.1)		2	(11.8)	
Influenza	0	(0.0)		1	(5.9)	
Pharyngitis	2	(11.1)		0	(0.0)	
Rhinorrhea	1	(5.6)		0	(0.0)	
Skin & Skin Appendage	3	(16.7)		1	(5.9)	
Alopecia	1	(5.6)		0	(0.0)	
Rash	1	(5.6)		1	(5.9)	
Rash, diaper	1	(5.6)		0	(0.0)	
Special Senses	2	(11.1)		5	(29.4)	
Otitis media	2	(11.1)		5	(29.4)	

* $p<0.05$ comparing famotidine 1.0 mg/kg/dose versus famotidine 0.5 mg/kg/dose.
N=Number of patients in the All Study Phases safety analysis per treatment group.
n (%): Number (percent) of patients in the indicated category.
Although a patient may have had 2 or more adverse experiences, the patient is counted only once within a category. The same patient may appear in different categories.
All body systems are listed in which at least 1 patient had an adverse experience.
[1] All patients are displayed as initially randomized, including those who underwent dose escalation.
DR = the number of patients having adverse experiences considered possibly, probably, or definitely drug related by the investigator.

Data Source: [4.8]

The most frequent adverse events included: otitis media (7 patients), agitation (5 patients), irritability (4 patients), upper respiratory infection (4 patients), fever (3 patients), constipation (3 patients) and somnolence (3 patients). The sponsor found that considering all study phases, the percentage of patients with an adverse experience was significantly greater (p=0.045) among those initially assigned to receive famotidine 1.0mg/kg/dose. Most events were not considered to be related to the study drug. Events considered study drug related included: agitation (5 patients), somnolence (3 patients), headache (2 patients), irritability (1 patient), anorexia (1 patient), hiccups (1 patient), oral candidiasis (1 patient).

After completion of the the Double-blind Phase of the study, 9 patients continued treatment with open-label marketed Famotidine Oral Suspension. Two of these patients experienced adverse events (1 diarrhea and rhinorrhea; 1 agitation).

The sponsor's two tables below summarize occurrence of clinical adverse events during the study with regard to patient disposition:

Table 37

Clinical Adverse Experience Summary—Observer-Blind Phase

Clinical adverse experiences (AEs)	Fam 0.5 mg (N=18)†		Fam 1.0 mg (N=17)†	
Number (%) of patients:	n	(%)	n	(%)
with one or more AEs	11	(61.1)	15	(88.2)
with no AE	7	(38.9)	2	(11.8)
with drug-related AEs	3	(16.7)	7	(41.2)
with serious AEs	0	(0.0)	0	(0.0)
with serious drug-related AEs	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)
discontinued due to an AE	2	(11.1)	4	(23.5)
discontinued due to a drug-related AE	2	(11.1)	4	(23.5)
discontinued due to a serious AE	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related AE	0	(0.0)	0	(0.0)

N=Number of patients in the Observer-Blind safety analysis per treatment group.
n (%): Number (percent) of patients in the indicated category.
† All patients are displayed as initially randomized, including those who underwent dose escalation.

Data Source: [4.8]

Table 38

Clinical Adverse Experience Summary--Double-Blind Phase

Clinical adverse experiences (AEs)	Fam 0.5 mg (N=7)[1]		Fam 1.0 mg (N=8)[1]		Placebo 0.5 mg (N=3)[1]		Placebo 1.0 mg (N=8)[1]	
Number (%) of patients:	n	(%)	n	(%)	n	(%)	n	(%)
with one or more AEs	3	(42.9)	2	(25.0)	1	(33.3)	6	(75.0)
with no AE	4	(57.1)	6	(75.0)	2	(66.7)	2	(25.0)
with drug-related AEs	1	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
with serious AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
with serious drug-related AEs	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to an AE	1	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a drug-related AE	1	(14.3)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
discontinued due to a serious drug-related AE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

[1] Patients are displayed according to the treatment received during the Double-Blind Phase.
N=Number of patients in the Double-Blind safety analysis per treatment group.
n (%): Number (percent) of patients in the indicated category.
Appendix [4.1.1] provides this display with dose-escalated patients placed according to initial randomization.

Data Source: [4.8]

During the Observer-Blind Phase of the study, 2 famotidine 0.5 mg patients discontinued due to adverse events (irritability, agitation) and 4 famotidine 1.0mg patients discontinued due to adverse events (decreased PO intake, somnolence, agitation [2]). In all these cases the events were felt to be related to study drug. No patients discontinued study treatment due to adverse events during the double-blind phase of the study. No adverse events were judged to be serious. There were no deaths during the study.

Laboratory evaluations were performed in some patients during the study (13 of 18 famotidine 0.5mg patients; 16 of 17 famotidine 1.0mg patients). Four patients had laboratory adverse events (decreased segmented neutrophils) during the study. These included 2 famotidine 0.5mg patients (1 during Observer-Blind Phase, 1 on Famotidine 0.5mg/kg/dose during Double-Blind Phase) and 2 famotidine 1.0mg patients (both on placebo in Double-Blind Phase). Counts returned to normal after discontinuation of the drug at completion of the study. These events were considered possibly study drug related.

Table 62

Details of Neutropenia—Laboratory Adverse Experience

Alloc. No.	Treatment Group	Relative Day	% Neutrophil	Segmented Neutrophil Count
1061	Fam 0.5 mg (twice daily)	1	15.8	1410
	Fam 0.5 mg (twice daily)	58	3	380
	Off Drug	62	17	2000
	Off Drug	69	12.2	-----
	Off Drug	76	26	2700
1065	Fam 1.0 mg (twice daily)	1	-----	-----
	Placebo 1.0 mg (twice daily)	58	25	1180
	Off Drug	86	18.6	1880
1075	Fam 0.5 mg (twice daily)	1	38	4880
	Fam 0.5 mg (twice daily)	58	7.3	710
	Off Drug	62‡	14	1300
1076	Fam 1.0 mg (twice daily)	1	13.4	1570
	Placebo 1.0 mg (twice daily)	35	4	470
	Off Drug	41	16	-----
	Off Drug	45‡	10.7	1200
	Off Drug	51‡	12†	-----
	Off Drug	62‡	21†	-----

† % granulocytes.
‡ Laboratory data received post case report form cutoff.

Data Source: [4.9]

No laboratory event was serious and no patients discontinued due to laboratory adverse events. Among patients who discontinued prematurely from the Observer-Blind Phase, no laboratory adverse experiences were found.

There were no striking differences between treatment groups in mean changes in vital signs or clinical laboratory parameters, including creatinine clearance (famotidine is cleared by the kidney), during the study. However, numbers of patients in each group were small.

Reviewer's comments: This was a two part safety study of famotidine in 35 infants aged <1year with a clinical diagnosis of GERD. In the first part of the study infants were randomized to receive famotidine at one of two dose levels. (A few patients received famotidine initially at the lower dose but were escalated to the higher dose because of lack of effectiveness). The majority of patients tolerated famotidine well in the Observer-blind Phase and upon completing

4 weeks of study drug were entered into a Double-blind treatment withdrawal phase. There were no apparent differences between treatment groups with regard to assessments of effectiveness of treatment. However, all patients appear to have had some improvement and numbers of patients were very small for this comparison. There were 4 cases of neutropenia that appeared to be treatment related and there were some adverse events that appeared to be treatment related (agitation, somnolence, headache, irritability, anorexia, hiccups, oral candidiasis). No events were serious. However, some patients did discontinue study drug because of adverse events (agitation, irritability, anorexia [decreased PO intake], somnolence).

There were no apparent differences in results with regard to gender or race in this study, but numbers of total patients and particlularly non-white patients were small.

This study provides mainly safety data on use of famotidine in these young pediatric patients. The narrative case histories suggest that patients though outpatients were carefully followed for adverse experiences, concurrent therapies, and symptoms related to GERD by means of telephone contact as well as scheduled and unscheduled clinic visits.

Possibly the symptomatology in this study was not severe enough to allow meaningful evaluation of beneficial drug effect. Also, the relatively short duration of treatment and the lack of an easily quantifiable measure of benefit further compromises the ability of this study to demonstrate efficacy of famotidine.

II. Protocol 129: Pharmacokinetics of Famotidine in Infants Up to 1 Year of Age

A. Study Description: This was an open-label, multicenter pharmacokinetic study of famotidine oral suspension in 24 infants <1 year of age who required treatment with famotidine or other H2-receptor antagonists. The study was conducted from 8/7/99 through 5/22/00 at 5 U.S. sites. The study consisted of two parts: Part 1 – comparison of pharmacokinetics of single intravenous famotidine dose (0.5mg/kg) in infants aged 0-3 months (Group I) and 3 to 12 months (Group II) versus a single oral dose of famotidine (0.5mg/kg) in infants age 0-12 months (Group III). Part 2 - comparison pharmacokinetics of two dose levels of famotidine (given intravenously or orally) given for up to 8 days to 12 infants ages 0-12 months.

The primary objective of the study was to compare the plasma clearance of famotidine in infants aged 0-3 months to that seen historically in older children. Additional objectives included: comparing plasma clearance of famotidine in infants 0-3 months to that in infants 3-12 months; assessing the relationship between famotidine plasma clearance and age and estimated creatinine clearance, and exploring pharmacokinetic/pharmacodynamic relationships in patients where possible.

B. Results: A total of 24 patients were enrolled in Part 1 and 12 patients in Part 2 (some patients participated in both parts of the study; for these patients the single dose data also is incorporated into the multiple dose data). All 24 patients received famotidine in Part 1 and 23 completed data collection. In Part 2 a total of 11 patients completed full dosing.

1. The sponsor's pharmacokinetic results are displayed in the following three tables:

   - Single-Dose: Pharmacokinetic parameters obtained after famotidine single dose administration are shown in the sponsor's table below:

Table 20

Geometric Mean (95% Confidence Intervals) Pharmacokinetic Parameters for Famotidine in Infants Aged 0 to 12 Months and Children Aged 11 to 15 Years Following Single 0.5-mg/kg Oral Dose of Famotidine

	Group III Infants (0 to 12 Mo) (n=5)	Children Aged 11 to 15 Yr[†] (n=8)	Geometric Means Ratio (Infants/Children) 95% CI	p-Value	MSE (log-scale)
$AUC_{0-\infty}$ (ng•hr/mL)	609	576	1.06	>0.25	-[‡]
C_{max} (ng/mL)	79.2	97.3	0.81	0.111	0.037
T_{max} (hr)[§]	2.0	2.3	-0.2[¶]	0.200	
Half-life (hr)	5.82	2.13	2.73	<0.01	0.053

[†] [1.1.11; 1.1.14].
[‡] Test statistic and confidence intervals based on between-subject variances in each age group.
[§] Median.
[¶] Difference (infants - children) and distribution-free 95% confidence interval based on Hodges-Lehmann estimation.
[¶] Observed minimum and maximum values.
Reported minimum and maximum values.

Data Source: [1.1.11; 1.1.14]

   - Single-Dose (2 dose levels): Pharmacokinetic parameters in infants as compared to older children at two different dose levels of famotidine are shown in the sponsor's table below:

Table 15

Geometric Mean (95% Confidence Intervals) Pharmacokinetic Parameters for Famotidine in Infants Aged 0 to 12 Months and Children Aged 1.1 to 12.9 Years Following a Single 0.3-mg/kg or 0.5-mg/kg IV Dose[†]

	Geometric Mean (95% CI)			Group I Versus Children			Group I Versus Group II		
	Group I Infants (0 to 3 Mo) (n=6)	Group II Infants (>3 to 12 Mo) (n=11)	Children Aged 1.1 to 12.9 Years (n=22)	Ratio (Group I/ Children) (95% CI)	p-Value	MSE (Log-Scale)	Ratio (Group I/ Group II) (95% CI)	p-Value	MSE (Log-Scale)
Clr (L/hr/kg)	0.14 (n=4) (0.09, 0.22)	0.29 (n=6) (0.20, 0.42)	0.38 (0.29, 0.50)	0.37 (0.21, 0.64)	<0.01	0.198	0.48 (0.26, 0.88)	0.021	0.198
Cl_r/Cl_p	0.81 (n=4) (0.55, 1.20)	0.78 (n=6) (0.56, 1.07)	0.64 (0.51, 0.81)	1.27 (0.81, 2.00)	>0.25	0.138	1.05 (0.63, 1.74)	>0.25	0.138
Half-life (hr)	7.60 (4.57, 12.63)	4.36 (3.61, 5.28)	2.65 (2.03, 3.46)	2.86 (1.62, 5.08)	<0.01	0.366	1.74 (1.26, 2.40)	<0.01	0.088
V_{dss} (L/kg)	1.76 (1.43, 2.18)	2.26 (1.93, 2.64)	1.53 (1.11, 2.10)	1.16 (0.82, 1.62)	>0.25	-[‡]	0.78 (0.60, 1.02)	0.064	0.059
$AUC_{0-\infty}$ (ng•hr/mL)	2578 (1884, 3527)	1084 (860, 1366)	NA				2.38 (1.61, 3.51)	<0.01	0.130
C_0 (ng/mL)	774 (594, 1009)	611 (503, 743)	NA				1.27 (0.91, 1.76)	0.146	0.093
$C_{12\ hr}$ (ng/mL)	59.1 (31.8, 109.7)	16.4 (10.2, 26.5)	NA				3.60 (1.64, 7.86)	<0.01	0.499
$C_{24\ hr}$ (ng/mL)	18.1 (7.1, 46.0)	1.9 (1.0, 3.8)	NA				9.40 (2.95, 29.92)	<0.01	1.145

[†] Infants received 0.5 mg/kg IV; children received either 0.3 mg/kg or 0.5 mg/kg IV as indicated in Table 13.
[‡] Test statistic and confidence interval based on between-subject variance in each age group.
NA—Not available.

Data Source: [1.1.7; 1.1.10; 1.1.12; 4.1.1]

- Multiple Dosing: Pharmacokinetic parameters obtained following multiple dosing are shown in the sponsor's table below:

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Least Squares Geometric Mean (95% Confidence Intervals) $AUC_{0-\tau}$[†] (ng•hr/mL) for Famotidine in Pediatric Patients Aged 0 to 12 Months After Multiple-Dose Administration Following 0.25-mg/kg IV (0.5 mg/kg P.O.) or 0.5-mg/kg IV (1.0 mg/kg P.O.) Doses

Dose (mg/kg)	N	Least Squares Estimate[‡] (95% CI)	Ratio (90% CI)	p-Value
0.25 IV	4	1475.4 (842.4, 2584.0)		
0.5 P.O.	2	775.6[§]		
0.25 IV + 0.5 P.O.	6	1190.7 (752.9, 1883.2)		
0.5 IV	4	4163.0 (2333.8, 7425.8)		
1.0 P.O.	1	1110.4[§]		
0.5 IV + 1.0 P.O.	5	3196.1 (1933.5, 5283.3)		
0.5 IV versus 0.25 IV			2.82 (1.48, 5.38)	0.021
(0.5 IV + 1.0 P.O.) versus (0.25 IV + 0.5 P.O.)			2.68 (1.56, 4.62)	0.012

† $AUC_{0\text{-}24\ hr}$ for infants dosed q24h; $AUC_{0\text{-}12\ hr}$ for infants dosed q12h.
‡ Based on 1-factor ANOVA with age included as covariate ; the mean age of 76.8 days (approximately 2½ months) of all infants included in the analysis was used in obtaining the least squares estimate for each dose.
§ Confidence interval not provided, due to small sample size.
Mean square error (log-scale) = 0.209.

Data Source: [4.1.5]

2. Pharmacodynamic parameters: Pharmacodynamic measurements were obtained in 6 infants. Predose gastric pH was 4 or above for 5 of the 6 patients. Pharmacodynamic data for these patients are shown in the sponsor's table below:

Table 37

Individual Values of Measures of Gastric pH Over 24 Hours in Infants Aged 0 to 12 Months Following Single and Multiple Doses of Famotidine

AN	Age (Days)	Day	Dose	Predose pH	pH Monitoring Interval	$AUC_{0\text{-last}}$ [H+] (mM*hr)	$AUC_{0\text{-last}}$ pH (pH*hr)	$AUC_{0\text{-}24\ hr}$ [H+] (mM*hr)	$AUC_{0\text{-}24\ hr}$ pH pH*hr)	Percentage of Time pH >4[†]	Percentage of Time pH >3[‡]	Number of Hours pH >4	Number of Hours pH >3
115	126	1	0.5 mg/kg IV	5.6	0 to 20.23 hr	0.026	120.1	--[§]	--[§]	100[§]	100[§]	20.23	20.23
401	17	1	0.5 mg/kg IV	4	0 to 35.9 hr	58.2	150.2	57.5	96.5	74.0	82.4	26.56	29.58
3002	58	1	0.25 mg/kg IV	4.9	0 to 4.02 hr	0.222	18.0	--[§]	--[§]	100[§]	100[§]	4.02	4.02
1010	58	1	0.25 mg/kg IV	3.0	0 to 24.08 hr	39.3	93.3	39.3	93.3	46.8	80.9	11.26	19.49
1006	30	1	0.25 mg/kg IV	5.5	0 to 24.02 hr	0.026	150.7	0.026	150.7	100	100	24.02	24.02
1006	34	4	0.5 mg/kg IV	7.5	0 to 35.97 hr	1.04	225.0	0.009	167.4	96.3	100	34.64	35.97

† Calculated as (number of hours pH>4)/(total number of hours pH monitored)—note that denominator differs from patient to patient.
‡ Calculated as (number of hours pH>3)/(total number of hours pH monitored)—note that denominator differs from patient to patient.
§ pH monitored for <24 hours.

Data Source: [4.1.9]

3. Safety: Seven patients in Part 1 reported a total of 14 adverse events and 5 patients in Part 2 reported a total of 12 adverse events. No events were considered to be related to study drug and no patients discontinued due to an adverse event during either part of the study. One patient in Part 1 had 2 serious events (cardiovascular disorder and respiratory disorder) and two patients in Part 2 had serious events (1, septicemia, hypotension and died; 1, septicemia but recovered). Other adverse events occurring in this study are listed in the Appendix.

   Three patients experienced 5 non-serious adverse laboratory experiences. These were: hypoproteinemia in 1 patient during Part 1, hemoglobin decreased in 1 patient on 1.2mg/kg/day famotidine during Part 2; and hyponatremia (2 episodes) and hyperglycemia in 1 patient on 2.8-5.6mg/kg/day famotidine during Part 2. No laboratory adverse events were serious and no patients discontinued treatment due to these events.

   There were no significant differences in changes in clinical laboratory values following single or multiple doses of famotidine.

C. Sponsor's conclusions: The sponsor concluded the following:

APPEARS THIS WAY
ON ORIGINAL

1. Famotidine systemic and renal clearance are reduced and half-life is prolonged in infants 0 to 3 months of age compared with the corresponding values in infants >3 to 12 months of age and previously reported studies in children older than 1 year and adults.

2. AUC values after oral administration of 0.5 mg/kg in infants are comparable to corresponding values in previously reported studies in children >1 year of age.

3. AUC values following single- and multiple-dose administration of 0.25 mg/kg IV and 0.5 mg/kg IV famotidine in infants aged 0 to 12 months decrease as the age of the infant increases. This effect is consistent with age-related maturation of renal function as supported by a decrease in AUC values as creatinine clearance increases.

4. Based on between-patient comparisons, AUC is increased 1.4-fold following single 0.5-mg/kg IV (or 1.0-mg/kg P.O.) doses compared with 0.25-mg/kg IV (or 0.5-mg/kg P.O.) doses. The corresponding increase in AUC following multiple dosing was 2.7-fold.

5. There was no evidence of accumulation with the 0.25-mg/kg IV or 0.5-mg/kg P.O. dose regimen adjusted by age for once-daily (infants <3 months) or twice-daily (infants >3 months) dosing.

6. The systemic bioavailability of famotidine in infants is approximately 42% based on between-patient comparisons after IV and oral dosing.

7. Of the 5 infants evaluated for pharmacodynamics, 2 infants 0 to 3 months of age with a gastric pH of 4 or less at baseline had gastric pH increase to >4 for 11 to 26 hours after famotidine doses of 0.25 and 0.5 mg/kg IV, respectively. This prolonged acid suppression is consistent with decreased clearance of famotidine.

8. Famotidine up to 0.5 mg/kg IV (or 1.0 mg/kg P.O.) given once daily (infants <3 months of age) or twice daily (infants >3 months of age) is generally well tolerated.

9. Based on these data, a dose regimen of 0.25 mg/kg IV or 0.5 mg/kg P.O. adjusted by age for once-daily (infants <3 months of age) or twice-daily (infants >3 months of age) dosing is a reasonable initial dose.

D. Reviewer's comments: Famotidine appeared to be generally well-tolerated by the infants in this study. However, numbers of patients were small and no definite conclusions as to the safety of famotidine in these infants can be made. The reasoning for the sponsor's selection of a dose to recommend for infants 0-12 months is not clear. The pharmacokinetic results of this study should be evaluated by FDA Clinical Pharmacology and Biopharmaceutics.

III. Protocol 130: Relative Bioavailability of the Famotidine Suspension 1mg/ml and Marketed PEPCID 40mg Tablets

This was an open-label, single center, single-dose, 2-period cross-over study of the bioavailability of investigational famotidine suspension in 24 healthy adult subjects. Each treatment period was separated by at least 7 days. The study was conducted from 11/11/99 to 11/23/99.

The sponsor's bioavailability results are summarized in the table below.

Geometric Means of Pharmacokinetic Parameters of Famotidine Following a Single Dose of PEPCID™ 40-mg Tablet or 40-mg Famotidine 1 mg/mL Oral Suspension (N=24)

	Tablet (A)	Suspension (B)	Ratio (B/A)	95% CI	p-Value	MSE (log-scale)
$AUC_{0-48\ hr}$ (ng hr/mL)	770.9	829.3	1.08	(0.97, 1.19)	0.159	0.0301
C_{max} (ng/mL)	136.2	147.0	1.08	(0.97, 1.20)	0.159	0.0328
T_{max} (hr)	1.50	2.00	0.25‡	(-0.25, 0.5)§	0.223	

† Median.
‡ Difference (B - A), based on Hodges-Lehmann estimation.
§ Distribution-free confidence interval, based on Hodges-Lehmann estimation.

Data Source: [4.1.5; 4.1.6]

There was one adverse event reported (dyspepsia). There were no serious adverse events and no patients discontinued study due to an adverse event.

Reviewer's comments: No pediatric patients were involved in this study. FDA Clinical Pharmacology and Biopharmaceutics should evaluate the bioavailability data.

IV. Protocol 136: Pharmacokinetics and Pharmacodynamics of Famotidine in Infants

A. Study description: This was a single center, open-label, single-dose pharmacokinetic/pharmacodynamic (gastric pH) study of famotidine 0.5mg/kg administered intravenously over 15 minutes in 12 neonates (ages 5-19 days). All patients completed the study.

B. Results: Sponsor's study results are summarized in the following tables:

Geometric Means (95% Confidence Intervals) of Pharmacokinetic Parameters of Famotidine in Infants Aged 5 to 19 Days and Children Aged 1.1 to 12.9 Years Following a Single IV Dose

	Infants Aged 5 to 19 Days[†] (n=10)	Children Aged 1.1 to 12.9 Years[‡] (n=22)	Ratio (Infants/ Children)	p-Value	MSE (log-scale)
Cl_p (L/hr/kg)	0.12 (0.07, 0.18)	0.42 (0.31, 0.56)	0.28 (0.16, 0.48)	<0.01	0.468
Clr (L/hr/kg)	0.08 (0.05, 0.11)	0.38 (0.26, 0.55)	0.20 (0.12, 0.35)	<0.01	0.360
Half-life (hr)	9.5 (6.5, 14.0)	2.7 (2.0, 3.4)	3.59 (2.25, 5.71)	<0.01	0.355
Vdss (L/kg)	1.29 (1.02, 1.62)	1.53 (1.11, 2.10)	0.84 (0.58, 1.23)	>0.25	-[§]
F_{el} (%)	66.3 (52.1, 84.3)	67.6 (53.7, 85.1)	0.98 (0.70, 1.37)	>0.25	0.133

[†] 0.5 mg/kg over 15 minutes.
[‡] 0.3 mg/kg bolus or 0.5 mg/kg over 15 minutes.
[§] Test statistic and confidence intervals based on between-subject variances in each age group.

Data Source: [1.1.10; 1.1.12; 4.1.1]

Table 8
Individual Values of Measures of Gastric pH Over 24 Hours in Infants Aged 5 to 19 Days Following a Single 15-Minute 0.5-mg/kg IV Dose of Famotidine

Patient	AUC		Percentage of Time pH :		Number of Hours pH :	
	H+ Concentration (mM*hr)	pH (pH*hr)	>4	>3	>4	>3
001	251.3	114.7	68.4	81.3	16.60	19.71
003	45.2	134.8	85.1	86.6	20.64	21.00
004	5.7	139.4	89.7	94.4	21.75	22.90
005	20.4	97.3	60.9	86.0	14.78	20.86
006	167.8	117.1	75.4	83.2	18.28	20.17
007	304.8	106.6	58.5	73.4	14.19	17.80
008	7.4	146.7	94.3	95.6	22.87	23.19
009	0.4	168.3	98.0	99.0	23.77	24.00
010	24.7	124.3	76.4	88.4	18.53	21.44
011	2.3	169.7	95.4	98.1	23.13	23.79
012	10.8	143.5	84.2	91.8	20.42	22.25
All Patients (n=11)						
Mean	76.4	132.9	80.6	88.9	19.5	21.6
(95% CI)			(71.3, 89.8)	(83.6, 94.2)	(17.3, 21.8)	(20.3, 22.8)
SD	111.0	23.6	13.8	7.8	3.3	1.9
Median	20.4	134.8	84.2	88.4	20.4	21.4
Geometric mean	19.1	131.0				
(95% CI)	(4.8, 75.6)	(116.2, 147.8)				
SD (log-scale)[*]	2.048	0.179				
Patients With Baseline pH < 4[‡] (n=9)						
Mean			83.5	90.7	20.2	22.0
(95% CI)			(73.6, 93.3)	(85.6, 95.7)	(17.9, 22.6)	(20.8, 23.2)
SD			12.8	6.6	3.1	1.6
Median			85.1	91.8	20.6	22.3

[*] Standard deviation of the natural log-transformed values.
[‡] Excludes AN 0007 and AN 0010 whose baseline pH values were >4.

Data Source: [4.1.1]

No clinical adverse events were reported and no patients discontinued study due to adverse events.

C. **Reviewer's comments:** It is not clear how thoroughly patients were monitored for adverse events. The protocol does not specify when and how adverse events were to be noted. However, a Medical/Adverse Event Form was included as part of the case report form used in the study. The protocol indicates "During the period of sample collection, routine monitoring of vital signs and urine output (ie., hourly) will be performed in accordance with clinical nursing protocols in place of the Neonatal Intensive Care Unit of the Arkansas Children's Hospital".

Safety Summary:
In the submitted studies famotidine appeared to be well-tolerated in most of the patients treated. The most frequent event judged by the investigator to be related to famotidine administration was agitation (5 patients in Study 131).

In the FDA AERS database (6/25/01) there are relatively few reports of serious adverse events in young pediatric patients, suggesting that serious adverse experiences in these patients are rare. Since the amount of usage of famotidine in these young pediatric patients is not precisely known, it is difficult to ascertain exact incidence of adverse events in these patients. Information from the AERS database is summarized in the following table:

AERS Database: Numbers of Pediatric Cases of Adverse Events Reported with Famotidine

	Number of patients (%)			
Outcome	Any event	Serious event*	Death	No outcome given
Total cases	9500 (100%)	1627 (100%)	329 (100%)	1302 (100%)
Cases age 0-<17 yrs	160[a](1.7%)	29[a](1.8%)	2 (0.6%)	15 (1.2%)
Cases age 0-36.4 mos	52[a] (0.5%)	13[a](0.8%)	2 (0.6%)	6 (0.5%)
Unknown age	1962 (20.7%)	88 (5.4%)	8 (2.4%)	627 ((48.1%)

* death, life-threatening, required hospitalization, congenital anomaly, and/or required intervention
[a] The AERS database had one case of a 65 year old woman coded as an infant. This patient is removed from these counts.

reviewer's original table

Seven of the patients with serious adverse events were <1 year of age. The adverse events experienced by these patients are summarized in the following table:

AERS Database: Serious Adverse Events in Pediatric Patients <1 Year of Age

Age	Gender	Event
1 month	Unknown	Congenital abnormality NOS
6 months	Female	Congenital abnormality NOS
3 months	Male	Congenital abnormality NOS, postmature baby
12 days	Female	Death
1 month	Unknown	Drug maladministration, overdose NOS
9 months	Female	Leucopenia NOS, haemoglobin decreased, blood urea nitrogen increased, blood urea nitrogen decreased blood creatinine increased, blood creatinine decreased, oliguria, anuria, blood lactate dehydrogenase increased, ascites, demylenation NOS, depressed level of consciousness, dermatitis NOS, hemolytic-uremic syndrome, hepatic failure, multi-organ failure, oedma NOS, thrombocytopenia, transaminases NOS increased, pericardial effusion, pleural effusion, pneumonia NOS, pyrexia. [patient died]
7 months	Female	Stevens-Johnson syndrome, mucous membrane disorder NOS, hepatocellular damage, pyrexia

NOS=not otherwise specified

Reviewer's original table

The two deaths were: (1) a preterm infant (23-24 wks) who was placed on I.V. famotidine deteriorated clinically and died at 12 days; concomitant medications included surfactant, steroids, antibiotics, fentanyl, and dopamine; physician judged death was not related to famotidine, and (2) a 9 month old infant with history of neurological disorder and growth retardation who was hospitalized for unclear reason and receiving multiple medications, including corticosteroids, phenobarbital, Trichloryl (ticlofos monosodium salt) and Venilon (immunoglobulins), received famotidine for prophylaxis of gastric ulceration and developed rash and fever; famotidine was discontinued (about 19 days after start); patient deteriorated, developed hepatic dysfunction, hemolytic-uremic syndrome, pleural effusion, pericardial effusion and ascites; renal function worsened requiring dialysis, patients developed pneumonia and respiratory function worsened and patient died due to multiple organ failure. A drug-lymphocyte stimulating test (DLST) was negative for famotidine and phenobarbital. The physician reported that the causal relationship between famotidine and hemolytic–uremic syndrome, fever, and rash was unknown. The causal relationship between famotidine and hepatic insufficiency was reported as "low". The causal relationship between famotidine and multiple organ failure was reported as "small".

Proposed Labeling Changes:
The sponsor's proposed labeling changes are shown and addressed below. The revised section is shown below with additions underlined and deletions struck out. Changes to tables are indicated in a "Note" before the table.

1. *Proposed:*

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS

Pharmacokinetics
Table 6 presents pharmacokinetic data from clinical trials and a published study in pediatric patients (<1 year of age; N=27) given famotidine I.V. 0.5 mg/kg and from published studies of small numbers of pediatric patients (1-15 years of age) given famotidine intravenously. Areas under the curve (AUCs) are normalized to a dose of 0.5 mg/kg I.V. for pediatric patients 1–15 years of age and compared with an extrapolated 40 mg intravenous dose in adults (extrapolation based on results obtained with a 20 mg I.V. adult dose).

[Note: Rows are added in Table 6 to give data regarding pharmacokinetic parameters of I.V. famotidine in patients <1year of age].

Table 6
Pharmacokinetic Parameters[a] of Intravenous Famotidine

Age (N=number of patients)	Area Under the Curve (AUC) (ng·hr/mL)	Total Clearance (Cl) (L/hr/kg)	Volume of Distribution (V_{ss}) (L/kg)	Elimination Half life ($T_{1/2}$) (hours)
0-1 month[c] (N=10)	NA	0.13 ± 0.06	1.4 ± 0.4	10.5 ± 5.4
0-3 months[d] (N=6)	2688 ± 847	0.21 ± 0.06	1.8 ± 0.3	8.1 ± 3.5
>3-12 months[d] (N=11)	1160 ± 474	0.49 ± 0.17	2.3 ± 0.7	4.5 ± 1.1
1-11 yrs (N=20)	1089 ± 834	0.54 ± 0.34	2.07 ± 1.49	3.38 ± 2.80
11-15 yrs (N=8)	1140 ± 320	0.48 ± 0.14	1.5 ± 0.4	2.3 ± 0.4
Adult (N=16)	1726[b]	0.39 ± 0.14	1.3 ± 0.2	2.83 ± 0.99

[a]Values are presented as means ± SD unless indicated otherwise.
[b]Mean value only.
[c]Single center study.
[d]Multicenter study.

Plasma clearance is reduced and elimination half-life is prolonged in pediatric patients 0-3 months of age compared to older pediatric patients. The pharmacokinetic parameters for pediatric patients, ages >3 months. ~~Values of pharmacokinetic parameters for pediatric patients, ages 1~~-15 years, are comparable to those obtained for adults.
Bioavailability studies of 8 pediatric patients (11-15 years of age) showed a mean oral bioavailability of 0.5 compared to adult values of 0.42 to 0.49. Oral doses of 0.5 mg/kg achieved AUCs of 645 ± 249 ng-hr/mL and 580 ± 60 ng-hr/mL in pediatric patients <1 year of age (N=5) and pediatric patients 11-15 years of age, respectively, compared to 482 ± 181 ng-hr/mL in adults treated with 40 mg orally.

Reviewer's comments: These changes have been reviewed by FDA Clinical Pharmacology and Biopharmaceutics and found acceptable.

2. *Proposed:*

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS

Pharmacodynamics

Pharmacodynamics of famotidine were evaluated in 5 pediatric patients 2-13 years of age using the sigmoid E_{max} model. These data suggest that the relationship between serum concentration of famotidine and gastric acid suppression is similar to that observed in one study of adults (Table 7).

Table 7
Pharmacodynamics of famotidine using the sigmoid E_{max} model

	EC_{50} (ng/mL)*
Pediatric Patients	28 ± 13
Data from one study	
a) healthy adult subjects	26.5 ± 10.3
b) adult patients with upper GI bleeding	18.7 ± 10.8

*Serum concentration of famotidine associated with 50% maximum gastric acid reduction. Values are presented as means ± SD.

~~Four~~ Five published studies (Table 8) examined the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients. While each study had a different design, acid suppression data over time are summarized as follows:

[Note: Added data on the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients <1 year of age to Table 8 and added age ranges to Table 8].

Table 8

Dosage	Route	Effect[a]	Number of Patients (age range)
0.5 mg/kg, single dose	I.V.	Gastric pH >4 for 19.5 hours (17.3, 21.8)[c]	11 (5-19 days)
0.3 mg/kg, single dose	I.V.	gastric pH >3.5 for 8.7 ± 4.7[b] hours	8 (2-7 years)
0.4-0.8 mg/kg	I.V.	gastric pH >4 for 8-9 hours	18 (2-69 months)
0.5 mg/kg, single dose	I.V.	a >2 pH unit increase above baseline in gastric pH for >8 hours	9 (2-13 years)
0.5 mg/kg b.i.d.	I.V.	gastric pH >5 for 13.5 ± 1.8[b] hours	4 (6-15 years)
0.5 mg/kg b.i.d.	oral	gastric pH >5 for 5.0 ± 1.1[b] hours	4 (11-15 years)

[a]Values reported in published literature.
[b]Means ± SD
[c]Mean (95% confidence interval)

The duration of effect of famotidine I.V. 0.5 mg/kg on gastric pH and acid suppression was shown in one study to be longer in pediatric patients <1 month of age than in older pediatric patients.

Reviewer's comment: These changes have been reviewed by FDA Clinical Pharmacology and Biopharmaceutics who recommended deletion of the second sentence of the last paragraph because of lack of supporting data.

3. Proposed:

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS

Reviewer's comment: This is a new section added under the "Clinical Pharmacology in Pediatric Patients" section. The section describes the design and results of Study 131.

This paragraph should be deleted. This study yielded essentially only additional safety information regarding famotidine in pediatric patients <1 year of age. The study was not designed or adequately powered to specifically demonstrate efficacy. The study results would be more appropriately included in the existing "Pediatric Patients" sub-section under **PRECAUTIONS.**

[redacted]

Reviewer's comments: This is a new sub-section under the ***PRECAUTIONS*** *section of the labeling. The sponsor has separated pediatric information into that for "Pediatric Patients <1 year of age" and that for "Pediatric Patients 1-16 years of age". This separation is acceptable, as the current submission contains a significant amount of information from well-documented studies of this population.*

The first paragraph has been reviewed by FDA Clinical Pharmacology and Biopharmaceutics and found to be acceptable. The sponsor should add as the first sentence of that paragraph the following: " Use of PEPCID in pediatric patients <1 year of age is supported by evidence from adequate and well-controlled studies of PEPCID in adults, and by the following studies in pediatric patients <1 year of age."

[redacted]

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

Conclusions and Recommendations:
In response to a Written Request for Pediatric Studies and in order to obtain provide labeling information on the use of famotidine in pediatric patients less than 1 year of age and obtain pediatric exclusivity (as per FDAMA), the sponsor has performed and submitted three pediatric studies. These studies involved pediatric patients less than 1 year of age who had symptoms of gastroesophageal reflux disease (e.g., vomiting (spitting up), irritability (fussing)). The studies include: a randomized, treatment withdrawal, clinical outcomes and safety study in pediatric patients less than 1 year of age (Study 131); a pharmacokinetic study in pediatric patients up to 1 year of age (Study 129); and a pharmacokinetic/pharmacodynamic study of intravenous famotidine in pediatric patients less than 1 month of age (Study 136). Also, a relative bioavailability study of oral tablet compared to oral suspension formulation in adults is submitted (Study 130). A total of 71 patients, 12 of whom were less than 1 month of age, were enrolled in these studies.

The sponsor has satisfied the requirements of the Written Request for Pediatric Studies and pediatric exclusivity has been granted.

This application provides useful information regarding use of famotidine in pediatric patients less than 1 year of age who have gastroesophageal reflux disease symptoms. Based on the information provided in these studies, this application is approvable.

The sponsor should revise the labeling as described in the Labeling section above.

cc:
NDA 19-462; 19-510; 19-527; 20-249; 20-958
HFD-180Division File
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/KRobie-Suh
HFD-180/PLevine
HFD-180/JChoudary
HFD-180/LZhou
HFD-720/TPermutt

APPENDIX

MK-0208 Prot. No.-129
Famotidine Infant PK Study

4. **Safety** (Cont.)

Table 38

Listing of Patients With Clinical Adverse Experiences—Part I

AN	Age (Days)	Total Daily Dose (mg)	Adverse Experience	Study Day	Duration	Intensity	Serious	Drug Related	Discontinued	Outcome
Part I Patients: Famotidine IV 0 to 3 Months										
0201	42	Off drug	Bowel sounds, abnormality	2	2 days	Mild	No	Probably not	No	Recovered
0302	21	Off drug	Rash, diaper	2	3 days	Moderate	No	Definitely not	No	Recovered
0303	30	1.5	Vomiting	1	1 day	Mild	No	Definitely not	No	Recovered
0304	27	1.8	Premature ventricular contractions	1	3 days	Mild	No	Probably not	No	Recovered
0305	35	Off drug	Edema, facial	2	12 days	Mild	No	Definitely not	No	Recovered
		Off drug	Edema, orbital	3	11 days	Mild	No	Definitely not	No	Recovered
		Off drug	Edema, swelling	3	11 days	Mild	No	Definitely not	No	Recovered
		Off drug	Cardiovascular disorder	3	11 days	Severe	Yes	Definitely not	No	Recovered
		Off drug	Edema, swelling	3	11 days	Mild	No	Definitely not	No	Recovered
		Off drug	Bowel sounds, abnormality	3	9 days	Mild	No	Definitely not	No	Recovered
		Off drug	Respiratory disorder	3	11 days	Severe	Yes	Definitely not	No	Recovered
Part I Patients: Famotidine IV 3 to 12 Months										
0110	162	Off drug	Fever	2	8 hrs	Mild	No	Definitely not	No	Recovered
0313	132	Off drug	Seizure disorder	2	5 mins	Moderate	No	Definitely not	No	Recovered
		Off drug	Edema laryngeal	2	1 day	Moderate	No	Definitely not	No	Recovered

Data Source: [4.9]

Table 39

Listing of Patients With Clinical Adverse Experiences—Part II

AN	Age (Days)	Total Daily Dose (mg)	Adverse Experience	Study Day	Duration	Intensity	Serious	Drug Related	Discontinued	Outcome
Part II Patients: 0.25 mpk IV (or 0.5 mg/kg P.O.)/0.25 mpk IV (0.5 mg/kg P.O.)										
3003	24	1.8	Bradycardia	3	2 days	Moderate	No	Probably not	No	Recovered
		1.8	Hypoventilation	3	2 days	Moderate	No	Probably not	No	Recovered
3008	110	5.6	Diarrhea	5	3 days	Moderate	No	Definitely not	No	Recovered
		5.6	Fever	7	5 days	Moderate	No	Definitely not	No	Still present
		Off drug	Septicemia	11	1 day	Severe	Yes	Definitely not	No	Recovered
Part II Patients: 0.25 mg/kg IV (or 0.5 mg/kg P.O.)/0.5 mg/kg IV (1.0 mg/kg P.O.)										
1006	30	1.4	Urinary tract infection	3	4 days	Moderate	No	Definitely not	No	Still present
		1.4	Hypotension	3	6 days	Severe	Yes	Definitely not	No	Recovered
		Off drug	Septicemia	11	2 days	Severe	Yes	Definitely not	No	Still Present
		Off drug	Death	12		Severe	Yes	Definitely not		
2004	78	1.0	Bradycardia	1	2 seconds	Mild	No	Probably not	No	Recovered
3007	275	7.4	Nervousness	5	6 days	Mild	No	Definitely not	No	Recovered
		7.4	Urinary tract infection	5	1 day	Mild	No	Definitely not	No	Still present

Data Source: [4.9]

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

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/s/

Kathy Robie-Suh
6/25/01 04:07:07 PM
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6/27/01 04:07:12 PM
MEDICAL OFFICER

Lilia Talarico
6/27/01 05:48:11 PM
MEDICAL OFFICER

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA:	20-958
Applicant:	Merck & Co. Inc.
Drug:	PEPCID™ Complete Tablets Famotidine and Calcium Carbonate/Magnesium Hydroxide Tablets Acid Reducer and Antacid ([FACT] Famotidine Antacid Coated Tablet) for over-the-counter (OTC) consumption
Indication:	Relieves Heartburn due to Acid Indigestion and Sour Stomach
Administration:	Coated Chewable Tablet - Chew 1 tablet thoroughly and swallow Up to 2 tablets in 24 hours, for up to 2 weeks
Material Reviewed:	Application, 11 volumes; data from one pharmacokinetic and two clinical studies; proposed OTC labeling; pertinent other information.
Reviewer:	Scheldon Kress, M.D./ May 5, 2000

Brief Overall Summary

The sponsor has requested approval of a new chewable 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 provide more rapid relief than famotidine alone and longer acting relief 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 the addition of antacid. It was also required that both beneficial effects be demonstrated in the same persons i.e., achieving successful benefit by all these criteria. In a prior submission dated 20 February, 1998 and reviewed by Dr. J. Senior (Jan 22, 1999), FACT demonstrated, in only one study (Protocol 110), faster relief of spontaneous induced heartburn than OTC famotidine and significantly longer relief than antacid or placebo. In this application, a confirming clinical study (Protocol 127) demonstrated that the combination therapy [FACT] is statistically superior to famotidine for onset of relief of heartburn symptoms and provides longer lasting duration of relief of heartburn symptoms compared to the antacid component alone. There was no increased safety risk. The contribution of the individual components has now demonstrated validity that the combination therapy [FACT] is better than each of the individual components and significantly better than placebo. Approval of the combination therapy is recommended.

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1. BACKGROUND

Famotidine is a potent, competitive, and reversible inhibitor of histamine action at the H2 receptor. Famotidine 10-mg FCT (film-coated tablet) is currently approved in the United States for the nonprescription short-term treatment of heartburn, acid indigestion and sour stomach, and for the prevention of these symptoms brought on by consuming food and beverages that are known to cause these symptoms. In daytime studies with meals, the duration of action of famotidine 10 mg is at least 9 hours, and current nonprescription labeling permits dosing up to twice a day. Famotidine is also approved in many countries, including the U.S., as a prescription agent for the treatment of active duodenal ulcer and gastric ulcer, maintenance therapy of duodenal ulcer disease for up to 1 year. and the long-term management of Zollinger-Ellison syndrome. In the U.S., the recommended dose of famotidine for the treatment of duodenal or benign gastric ulcer is 40 mg P.O. once daily at night. Over 11,000 patients have received famotidine in controlled trials performed worldwide. Famotidine has been well tolerated in these studies. Side effects have generally been mild and have been predominantly headache, constipation, diarrhea, and dizziness.

The rationale to develop a combination antacid/H_2-receptor antagonist can be summarized as follows: single doses of antacid alone and famotidine alone are expected to relieve heartburn more effectively than placebo. Although both agents are believed to act by reducing intraluminal acidity, their mechanisms of action and pharmacodynamic profiles differ substantially. Antacids are believed to work rapidly by neutralizing intraluminal acid on contact. Their duration of action is limited by physiologic clearing mechanisms. Famotidine reduces gastric acid production via antagonism of the histamine H_2-receptor. famotidine 10 mg is believed to require a longer time to onset of pharmacodynamic effect, but to have an appreciably longer duration of effect than traditional antacids. These differences suggest that a combination of famotidine and antacid in one product would potentially offer the benefits of more rapid relief of symptoms than famotidine alone, and a longer duration of relief than antacid alone.

Antacids have been the standard of therapy for nonprescription treatment of acid related symptoms. Recent pharmacodynamic data with high-dose liquid antacids suggest that the duration of their effect may be approximately 2 hours in the esophagus, and may depend on the excipients chosen. The duration of action is also limited by physiologic clearing mechanisms (e.g., esophageal and/or gastric emptying). This limited duration of action may result in the need for frequent redosing in order to control symptoms.

Given their differing mechanisms of action, the sponsor set out to prove that a fixed combination of famotidine and antacid may provide the benefits of more rapid relief of symptoms than famotidine alone, and a longer duration of relief than antacid alone. Johnson & Johnson - Merck Consumer Pharmaceuticals Co. developed a coated-chewable tablet (CCT) that contained famotidine 10 mg, $CaCO_3$ 800 mg, and $Mg(OH)_2$ 165 mg [FACT]. The antacid component of this tablet provides 21 mEq of acid-neutralizing capacity (ANC). This ANC is within the

range of doses typically used in OTC antacid products for treatment of intermittent heartburn (11 to 55 mEq).

Application Background

The requirements for efficacy were not adequately demonstrated in the prior submitted clinical studies for this product. Only prior Study 110 meet the necessary criteria by demonstrating 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. A Non-Approvable Letter was issued on February 19, 1999.

This application presents the results of an additional clinical study Protocol 127 which was set to replicate the results of Protocol 110, submitted as confirmation of the results of Protocol 110. Therefore, it is submitted in consideration as the second adequate and well controlled trial that demonstrates the superiority of the combination relative to each of the individual components. 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).

In a combination therapy, the contributions of the individual components of the combination therapy, the validity of the study design, and internal consistency of the results must be demonstrated. The contribution of the individual components is demonstrated by showing that the combination therapy (FACT) is better than each of the individual components [21 CFR 300.50(a)]; i.e., FACT is better than the famotidine component alone for onset of adequate relief and better than the antacid component alone for duration of adequate relief. Validity and internal consistency are demonstrated by showing that both the individual components and the combination therapy are significantly better than placebo.

2. STUDY DESIGN – PROTOCOL 127

Protocol 127 was a multicenter, double-blind, randomized, parallel-group, multiple-dose clinical study designed to compare the efficacy of famotidine/antacid combination tablet, famotidine 10 mg, antacid and placebo in patients with frequent heartburn.

The study was designed to evaluate both the onset and duration of symptom relief with the fixed combination of famotidine and antacid. A single-blind antacid run-in period was used to confirm that the randomized patients were frequent heartburn sufferers who generally responded to OTC treatment. Relief of heartburn was assessed at multiple timepoints within the first hour post-dose in order to demonstrate the hypothesized onset advantage for the combination relative to famotidine. Relief ratings were collected hourly from 60 minutes to 8 hours post-dose to examine whether the combination relieved heartburn for a longer period of time than antacid. Four episodes were treated in a naturalistic setting so that the efficacy of first and subsequent doses could he examined. Protocol 127, like Protocol 110, used the double dummy technique to maintain the double blinding.

Protocol Title: A Double-Blind Randomized. Parallel-group, Multiple-Dose Study to Compare the Efficacy of Famotidine/antacid Combination (FACT), Famotidine 10 mg, Antacid, and Placebo in Patients With Frequent Heartburn (Study # 2)

Investigator(s) / Study Centers: Thirty-two investigators in the United States
Study Time Period: 9-Mar-1999 thru 22 July-1999
Clinical Phase III MK-0208C Protocol 127
Duration of Therapy:

Run-in-period: one week single-blind antacid baseline
Study-period: two week double-blind therapy 4 doses, taken as required.

Objectives: To compare the efficacy of famotidine/antacid combination coated chewable tablet (FACT), famotidine 10-mg film coated table (FCT), antacid 21 mEq, and placebo in patients with frequent heartburn

STUDY DESIGN: Randomized. double-blind, placebo-controlled, multicenter trial with 4 parallel groups.

DOSAGE/FORMULATION: Each patient took a single dose consisting of 1 coated chewable tablet and 1 film-coated tablet for 4 doses.

STUDY POLPULATION: This consisted of male and female patients at least 18 years of age with a history of food-induced heartburn of at least 2 months' duration with at least 3 episodes per week. Patients must have used antacids or OTC acid reducers for effective relief of their symptoms.

EVALUATION CRITERIA - EFFICACY:

Primary Parameters: The treatment groups were compared with respect to:

- the time to adequate symptom relief for ONSET OF ACTION
- the DURATION of adequate symptom relief during the 8-hour post-dose observation period across each patient's 4 episodes of heartburn. (Duration was defined as the first time interval after onset when a patient reported no adequate relief, or required rescue medication).

Primary Comparisons:

- Famotidine/antacid combination versus famotidine 10-mg FCT was considered the primary treatment comparison for onset (1)
- Famotidine/antacid combination versus antacid 21 mEq was considered the primary treatment comparison for duration.(2)

Secondary Parameters: The treatment groups were also compared with respect to

- GLOBAL EVALUATION (collected at the final visit).(3)

Exploratory Parameters: The treatment groups were also compared with respect to

- TIME TO RESCUE MEDICATION,(4)
- Proportion of episodes considered SUCCESSFUL TREATMENT for both onset and duration.(5) Four different definitions of a "successfully treated" episode were used where only the time point of the definition varied. Specifically, "successfully treated" for the "onset" portion was defined as adequate relief at 15, 30, 45, or 60 minutes after dosing. All four definitions used the same success criteria for the "duration" portion of the definition, i.e.. adequate relief sustained through 8 hours post-dose, and requiring no rescue medication at any time after dosing.

Definitions:

- Time to adequate relief - number of episodes 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
- Episodes with adequate relief - number of episodes first occurring at each of the following 6 time points: 15 minutes, 30 minutes, 45 minutes, 1 hour, 2 hours, and >2 hours
- Analysis of duration of adequate relief - number of episodes with adequate relief sustained through each of the following 6 time points: >7 hours, 6 to 7 hours, 5 to 6 hours, 4 to 5 hours, <4 hours, and "no onset of adequate relief."
- Analysis of time to rescue medication - patient data consisted of the number of episodes with rescue medication first used at each of the following 6 time points: <1 hour, <2 hours, <-4 hours, <6 hours, <8 hours, and no rescue needed
- Successfully treated - number of episodes of adequate relief that occurs within 15 (30, 45, or 60) minutes and was sustained through 8 hours post-dose (number of episodes in each of two categories (i.e., binary data: "successfully treated" and "not successfully treated.")

The numerical values established to score the six timepoints measuring onset and duration are shown in Table 1.

Table 1
Protocol # 127
Numeric Values to the Six Timepoints
Of the Onset and Duration Analysis

Value	Onset	Duration
5	15 mins	> 7 Hrs
4	30 mins	6 Hrs
3	45 mins	5 Hrs
2	60 mins	4 Hrs
1	120 mins	< 4 Hrs
0	>120 mins	No Onset

Safety

Adverse experiences were recorded from the first dose of baseline antacid through the end of the study period.

Patient Selection

Inclusion Criteria

1) Males or females who were at least 18 years of age or older. Patients were cooperative, reliable, and of adequate intelligence to grade and record symptoms as requested.

2) History of food-induced heartburn of at least 2 months duration with at least 3 episodes per week. Patients were able to identify specific foods or beverages that produce their heartburn and they used antacids or OTC acid reducers for effective relief of their discomfort.

3) Patients must have signed the informed consent after the nature of the study was fully explained and before any procedures dictated by this protocol were performed.

Exclusion Criteria

Patients were excluded from participation in the study if they met any of the following:

1) Had a history of a serious medical condition or evidence of impaired renal function.

2) Had a history of duodenal ulcer, gastric ulcer, atrophic gastritis, or diverticulitis within the 2 years prior to study start; history of upper GI tract surgery or vagotomy, esophageal strictures, Barrett's esophagus, endoscopically identified erosive esophagitis of moderate

or greater severity, Zollinger-Ellison syndrome, inflammatory bowel disease, or was known to have gallstones.

3) Were pregnant or lactating. Women of childbearing potential were instructed to use adequate means of contraception.

4) Recently used (within 1 week of entering baseline run-in period) prescription sucralfate, nizatidine, cimetidine, ranitidine, famotidine, cisapride, metoclopramide, misoprostol, or any other prescription medication which modifies acid secretion. In addition, recent chronic use of nonsteroidal anti-inflammatory drugs, orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, and antineoplastics were prohibited.

5) Recent use (within 4 weeks of baseline ran-in period) of omeprazole or lansoprazole.

6) Patient received any form of oral tetracycline.

7) Patient began nicotine replacement therapy during the study.

8) Had a recent history of habituating drug or alcohol abuse, psychosis, or other condition which made the patient unlikely to comply with the protocol.

9) Patient used an investigational drug within 30 days prior to start of this study or within five half-lives of the investigational drug, whichever was longer.

10) Patient had a prior adverse reaction to antacids, H2 antagonists, or any of the components of the study medication.

11) Other conditions which would have interfered with data interpretation or created undue risk.

12) Previous participation in a heartburn study within the 3 months prior to study start.

13) Only one person per household was permitted to participate in the double-blind period.

14) Study personnel and immediate relatives of study personnel were not permitted to participate.

Summary of Study Design

This was a multicenter, double-blind, double-dummy, randomized, parallel (n=400/group), multiple-dose study. The study medications assessed were FACT (famotidine 10 mg/antacid 21 mEq calcium carbonate-magnesium hydroxide), antacid 21 mEq (calcium carbonate-magnesium hydroxide), famotidine 10-mg FCT, and placebo. Treatments were self-administered for 4 spontaneously occurring heartburn episodes. The original protocol specified that approximately 2800 patients were anticipated to be enrolled at 28 study centers in a single-blind 7-day antacid run-in period to obtain 1600 frequent heartburn sufferers eligible for randomization to double-blind medication. In actuality, 2429 patients were enrolled at 32 study centers.

During the run-in period, patients had 30 antacid tablets (24 mEq ANC each) to self-treat their heartburn episodes. They recorded the time and date of each tablet taken and whether they had adequate relief at 4 time points over the first hour post-dose. Patients returned to the clinic at the completion of the run-in week when the study coordinator reviewed the diary card, medication consumption, and adverse events. Unused study medication was returned. Patients satisfying all of the following criteria were eligible to enter the double-blind period:

- used study medication on $\geq$ 3 of the 7 days (defined as 6 AM to 6 AM)
- took 2 doses of study medication within a 24-hour period
- had adequate relief of their heartburn within 1 hour of dosing for greater than or equal to 50% of the episodes
- satisfactorily completed the diary card.

Patients who did not meet the above criteria were dismissed from the study.

Eligible patients were randomized and received study instructions, a diary card, a box containing four blister cards of study medication, and rescue antacid. Patients were instructed to use the study medication to treat each heartburn episode, not to take a second dose of study medication for at least 8 hours, and not to take more than 2 doses of study medication in any single 24-hour period. Patients were permitted to take the rescue antacid provided between 1 and 8 hours post-dose if their heartburn symptoms had not begun to decrease. Patients were told that they could not eat, drink, sleep, or lie down for the first hour post-dose, and that if they ate or drank during the 8-hour assessment period, they had to record the time that they consumed the food or beverage.

When patients experienced a spontaneous episode of heartburn, they assessed their heartburn on a 3-point scale (mild, moderate, or severe), self-administered their study medication (2 tablets), and assessed the adequacy of heartburn relief (yes or no) every 15 minutes for the first hour and then hourly (yes, no, or sleeping) between 1 and 8 hours post-dose. If patients required rescue medication, they recorded the time of the administration. Patients returned to the clinic within 5 days of the completion of the 14-day double-blind period, when the study

coordinator reviewed the diary card, medication consumption, and adverse events. The patient's overall global assessment of study medication was recorded using a 5-point scale at this visit. Drug packaging, unused medication, and timers were returned.

Treatment Plan

Run-In Period - Each patient received a bottle containing 30 doses of green mint-flavored single-blind antacid 24 mEq ANC. Water (2 ounces) was allowed for administration of thc single-blind antacid.

Double-Blind Period - Each patient received 4 doses of one of the following treatments according to a computer-generated allocation schedule :

- Famotidine 10-mg/antacid 21-mEq combination CCT (coated chewable tablet) (FACT)
- Famotidine 10-mg FCT (film-coated tablet)
- Antacid 21-mEq CCT
- Placebo

To maintain the double-blind study conditions, matching placebos (double dummy) were supplied as indicated in Table 2. FACT appeared identical to the Antacid CCT. A single dose consisted of 2 tablets: 1 CCT followed by I FCT in that order. Water (2 ounces) was allowed for administration of the film-coated tablet. The CCT was thoroughly chewed before swallowing; the FCT was swallowed with water. Patients were encouraged to take all 4 doses during the 2-week double-blind period.

Table 2
Clinical Supplies

Treatment Groups	Formulation Numbers	Tablet A	Tablet B
A. Famotidine/antacid combination	C-675-8C	1 famotidine/antacid combination CCT	1 placebo FCT
B. Famotidine 10 mg	C-681-1W	1 antacid placebo CCT	1 famotidine 10-mg FCT
C. Antacid 21 mEq	C-659-1B	1 antacid 21 mEq ANC CCT	1 placebo FCT
D. Placebo	Antacid placebo- C-657-1C Famotidine FCT placebo- C-728-1D	1 antacid placebo CCT	1 placebo FCT

The instruction for Tablet A read "Chew Tablet A thoroughly and swallow." The instruction for Tablet B read "Then swallow (do not chew) Tablet B with 2 ounces of water."