

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-462/S-030

19-527S-024

20-752/S-005

Trade Name: Pepcid Tablets
Pepcid for Oral Suspension
Pepcid RPD for Orally Disintegrating Tablets

Generic Name: Famotidine

Sponsor: Merck & Company, Inc.

Approval Date: June 6, 2002

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20-752/S-005

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	X
Approvable Letter	X
Final Printed Labeling	X
Medical Review(s)	X
Chemistry Review(s)	X
EA/FONSI	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	X
Administrative Correspondence Document(s)	X

**CENTER FOR DRUG EVALUATION AND
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APPLICATION NUMBER:

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APPROVAL LETTER



NDA 19-462/S-030
NDA 19-527/S-024
NDA 20-752/S-005

Merck and Co., Inc.
Attention: Virginia G. Snyder
Manager, Regulatory Affairs
c/o Merck Research Laboratories (BLA-20)
Sumneytown Pike, P.O. Box 4
West Point, PA 19486

Dear Ms. Snyder:

Please refer to your supplemental new drug applications dated August 28, 2000, received August 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA 19-462/S-030: Pepcid™ (famotidine) Tablets
NDA 19-527/S-024: Pepcid™ (famotidine) for Oral Suspension
NDA 20-752/S-005: Pepcid RPD™ (famotidine) Orally Disintegrating Tablets

We acknowledge receipt of your submissions dated July, 02; and August 10, 2001. Your submission of August 10, 2001 constituted a complete response to our June 28, 2001 action letter.

These supplemental new drug applications for Pepcid™ provide for changes to the following sections of the currently approved labeling: CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS. These applications include study reports in support of a six-month extension to patent protection based upon pediatric exclusivity as well as information regarding the bioavailability of the famotidine oral formulations used in the studies and information concerning the safety of famotidine use in infants.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted final printed labeling (package insert submitted August 10, 2001). Accordingly, these supplemental applications are approved effective on the date of this letter.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We note that you have fulfilled the pediatric study requirement at this time.

NDA 19-462/S-030
NDA 19-527/S-024
NDA 20-752/S-005

Page 2

In addition, please submit three copies of the introductory promotional materials that you propose to use for these products. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package inserts directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Victor F. C. Raczkowski, M.D., M.Sc.
Acting Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment:

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Victor Raczkowski
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-462/S-030

19-527/S-024

20-752/S-005

APPROVABLE LETTER



NDA 19-462/S-030
NDA 19-527/S-024
NDA 20-752/S-005

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

Please refer to your supplemental new drug applications dated August 28, 2000, received August 28, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for

NDA 19-462/S-030: Pepcid™ (famotidine) Tablets
NDA 19-527/S-024: Pepcid™ (famotidine) for Oral Suspension
NDA 20-752/S-005: Pepcid RPD™ (famotidine) Orally Disintegrating Tablets

These supplemental new drug applications for Pepcid™ provide for changes to the following sections of the currently approved labeling: CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS. These applications include study reports in support of a six-month extension to patent protection based upon pediatric exclusivity as well as information regarding the bioavailability of the famotidine oral formulations used in the studies and information concerning the safety of famotidine use in infants

We have completed the review of these applications, and it is approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

1. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS**, delete the sentence: _____

2. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS**, delete the new sub-section titled: | _____ |
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. Enrolled patients were diagnosed primarily by history of vomiting (spitting up) and irritability (fussiness). The famotidine dosing regimen was once daily for patients <3 months of age and twice daily for patients 3 to 10.5 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 to 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.)

In addition, provide information regarding _____

4. Under **PRECAUTIONS**, in the new sub-section: Pediatric patients <1 year of age:
 - a. 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.”
 - b. 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.”

5. 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).”

In addition, include information regarding _____

6. 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."

In addition, all previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend these supplemental applications, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the applications. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the applications may be approved.

These products may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if they are marketed with these changes prior to approval of these supplemental applications.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Project Manager, at (301) 827-7310.

Sincerely,

{See appended electronic signature page}

Lilia Talarico, M.D.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Lilia Talarico
6/28/01 04:42:41 PM

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-462/S-030

19-527/S-024

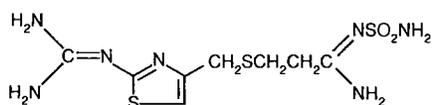
20-752/S-005

APPROVED LABELING

PEPCID®
(FAMOTIDINE) TABLETS
PEPCID®
(FAMOTIDINE) FOR ORAL SUSPENSION
PEPCID RPD®
(FAMOTIDINE) ORALLY DISINTEGRATING TABLETS

DESCRIPTION

The active ingredient in PEPCID* (famotidine) is a histamine H₂-receptor antagonist. Famotidine is *N*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide. The empirical formula of famotidine is C₈H₁₅N₇O₂S₃ and its molecular weight is 337.43. Its structural formula is:



Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol.

Each tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: hydroxypropyl cellulose, hydroxypropyl methylcellulose, iron oxides, magnesium stearate, microcrystalline cellulose, corn starch, talc, and titanium dioxide.

Each Orally Disintegrating Tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: aspartame, mint flavor, gelatin, mannitol, red ferric oxide, and xanthan gum.

Each 5 mL of the oral suspension when prepared as directed contains 40 mg of famotidine and the following inactive ingredients: citric acid, flavors, microcrystalline cellulose and carboxymethylcellulose sodium, sucrose and xanthan gum. Added as preservatives are sodium benzoate 0.1%, sodium methylparaben 0.1%, and sodium propylparaben 0.02%.

CLINICAL PHARMACOLOGY IN ADULTS

GI Effects

PEPCID is a competitive inhibitor of histamine H₂-receptors. The primary clinically important pharmacologic activity of PEPCID is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCID, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, PEPCID inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. After oral administration, the onset of the antisecretory effect occurred within one hour; the maximum effect was dose-dependent, occurring within one to three hours. Duration of inhibition of secretion by doses of 20 and 40 mg was 10 to 12 hours.

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84%, respectively, 3 to 5 hours after administration, and 25% and 30%, respectively, 8 to 10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6-8 hours. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of PEPCID to mean values of 5.0 and 6.4, respectively. When PEPCID was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of PEPCID was raised to about 5.

PEPCID had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by PEPCID.

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Other Effects

Systemic effects of PEPCID in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted. (See ADVERSE REACTIONS.) Serum hormone levels, including prolactin, cortisol, thyroxine (T_4), and testosterone, were not altered after treatment with PEPCID.

Pharmacokinetics

PEPCID is incompletely absorbed. The bioavailability of oral doses is 40-45%. PEPCID Tablets, PEPCID for Oral Suspension and PEPCID RPD Orally Disintegrating Tablets are bioequivalent. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. PEPCID undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of PEPCID in plasma is protein bound. PEPCID has an elimination half-life of 2.5-3.5 hours. PEPCID is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide.

There is a close relationship between creatinine clearance values and the elimination half-life of PEPCID. In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours and adjustment of dose or dosing intervals in moderate and severe renal insufficiency may be necessary (see PRECAUTIONS, DOSAGE AND ADMINISTRATION).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (see PRECAUTIONS, *Geriatric Use*).

Clinical Studies

Duodenal Ulcer

In a U.S. multicenter, double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered PEPCID was compared to placebo. As shown in Table 1, 70% of patients treated with PEPCID 40 mg h.s. were healed by week 4.

Table 1
Outpatients with Endoscopically
Confirmed Healed Duodenal Ulcers

	PEPCID 40 mg h.s. (N = 89)	PEPCID 20 mg b.i.d. (N = 84)	Placebo h.s. (N = 97)
Week 2	**32%	**38%	17%
Week 4	**70%	**67%	31%

**Statistically significantly different than placebo ($p < 0.001$)

Patients not healed by week 4 were continued in the study. By week 8, 83% of patients treated with PEPCID had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with PEPCID was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving PEPCID than for patients receiving placebo; patients receiving PEPCID also took less antacid than the patients receiving placebo.

Long-Term Maintenance

Treatment of Duodenal Ulcers

PEPCID, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with PEPCID. The 89 patients treated with PEPCID had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo ($p < 0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with PEPCID was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p < 0.01$).

Gastric Ulcer

In both a U.S. and an international multicenter, double-blind study in patients with endoscopically confirmed active benign gastric ulcer, orally administered PEPCID, 40 mg h.s., was compared to placebo h.s. Antacids were permitted

during the studies, but consumption was not significantly different between the PEPCID and placebo groups. As shown in Table 2, the incidence of ulcer healing (dropouts counted as unhealed) with PEPCID was statistically significantly better than placebo at weeks 6 and 8 in the U.S. study, and at weeks 4, 6 and 8 in the international study, based on the number of ulcers that healed, confirmed by endoscopy.

Table 2
 Patients with Endoscopically
 Confirmed Healed Gastric Ulcers

	U.S. Study		International Study	
	PEPCID 40 mg h.s. (N=74)	Placebo h.s. (N=75)	PEPCID 40 mg h.s. (N=149)	Placebo h.s. (N=145)
Week 4	45%	39%	†47%	31%
Week 6	†66%	44%	†65%	46%
Week 8	***78%	64%	†80%	54%

***,† Statistically significantly better than placebo ($p \leq 0.05$, $p \leq 0.01$ respectively)

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving PEPCID than for patients receiving placebo; however, in neither study was there a statistically significant difference in the proportion of patients whose pain was relieved by the end of the study (week 8).

Gastroesophageal Reflux Disease (GERD)

Orally administered PEPCID was compared to placebo in a U.S. study that enrolled patients with symptoms of GERD and without endoscopic evidence of erosion or ulceration of the esophagus. PEPCID 20 mg b.i.d. was statistically significantly superior to 40 mg h.s. and to placebo in providing a successful symptomatic outcome, defined as moderate or excellent improvement of symptoms (Table 3).

Table 3
 % Successful Symptomatic Outcome

	PEPCID 20 mg b.i.d. (N=154)	PEPCID 40 mg h.s. (N=149)	Placebo (N=73)
Week 6	82††	69	62

†† $p \leq 0.01$ vs Placebo

By two weeks of treatment symptomatic success was observed in a greater percentage of patients taking PEPCID 20 mg b.i.d. compared to placebo ($p \leq 0.01$).

Symptomatic improvement and healing of endoscopically verified erosion and ulceration were studied in two additional trials. Healing was defined as complete resolution of all erosions or ulcerations visible with endoscopy. The U.S. study comparing PEPCID 40 mg p.o. b.i.d. to placebo and PEPCID 20 mg p.o. b.i.d. showed a significantly greater percentage of healing for PEPCID 40 mg b.i.d. at weeks 6 and 12 (Table 4).

Table 4
 % Endoscopic Healing - U.S. Study

	PEPCID 40 mg b.i.d. (N=127)	PEPCID 20 mg b.i.d. (N=125)	Placebo (N=66)
Week 6	48†††.‡‡	32	18
Week 12	69†††.‡	54†††	29

††† $p \leq 0.01$ vs Placebo

‡ $p \leq 0.05$ vs PEPCID 20 mg b.i.d.

‡‡ $p \leq 0.01$ vs PEPCID 20 mg b.i.d.

As compared to placebo, patients who received PEPCID had faster relief of daytime and nighttime heartburn and a greater percentage of patients experienced complete relief of nighttime heartburn. These differences were statistically significant.

In the international study, when PEPCID 40 mg p.o. b.i.d., was compared to ranitidine 150 mg p.o. b.i.d., a statistically significantly greater percentage of healing was observed with PEPCID 40 mg b.i.d. at week 12 (Table 5). There was, however, no significant difference among treatments in symptom relief.

Table 5
 % Endoscopic Healing - International Study

	PEPCID 40 mg b.i.d. (N=175)	PEPCID 20 mg b.i.d. (N=93)	Ranitidine 150 mg b.i.d. (N=172)
Week 6	48	52	42
Week 12	71 ^{†††}	68	60

^{†††} p<0.05 vs Ranitidine 150 mg b.i.d.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, PEPCID significantly inhibited gastric acid secretion and controlled associated symptoms. Orally administered doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. PEPCID was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence which were considered to be due to the drug.

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).

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 _d) (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 ± 2.60
11-15 yrs (N=6)	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

^aValues are presented as means ± SD unless indicated otherwise.

^bMean value only.

^cSingle center study.

^dMulticenter 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-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 in pediatric patients 11-15 years of age, respectively, compared to 482 ± 181 ng-hr/mL in adults treated with 40 mg orally.

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

EC₅₀ (ng/mL)*

Pediatric Patients 26 ± 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.

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:

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	6 (2-7 years)
0.4-0.8 mg/kg	I.V.	gastric pH >4 for 6-9 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)

^aValues reported in published literature.

^bMeans ± SD.

^cMean (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. This longer duration of gastric acid suppression is consistent with the decreased clearance in pediatric patients <3 months of age (see Table 6).

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most adult patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.
 2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies in adults have not extended beyond one year.
 3. *Short term treatment of active benign gastric ulcer.* Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.
 4. *Short term treatment of gastroesophageal reflux disease (GERD).* PEPCID is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).
- PEPCID is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).
5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)* (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

CONTRAINDICATIONS

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, PEPCID should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

PRECAUTIONS

General

Symptomatic response to therapy with PEPCID does not preclude the presence of gastric malignancy.

Patients with Moderate or Severe Renal Insufficiency

Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, longer intervals between doses or lower doses may need to be used in patients with moderate (creatinine clearance

<50 mL/min) or severe (creatinine clearance <10 mL/min) renal insufficiency to adjust for the longer elimination half-life of famotidine (see CLINICAL PHARMACOLOGY IN ADULTS and DOSAGE AND ADMINISTRATION).

Information for Patients

The patient should be instructed to shake the oral suspension vigorously for 5-10 seconds prior to each use. Unused constituted oral suspension should be discarded after 30 days.

Patients should be instructed to leave the PEPCID RPD Orally Disintegrating Tablet in the unopened package until the time of use. Patients should then open the tablet blister pack with dry hands, place the tablet on the tongue to dissolve and be swallowed with saliva. No water is needed for taking the tablet.

Phenylketonurics: Phenylketonuric patients should be informed that PEPCID RPD contains phenylalanine 1.05 mg per 20 mg orally disintegrating tablet and 2.10 mg per 40 mg orally disintegrating tablet.

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man, in animal models, and *in vitro* have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2000 mg/kg/day (approximately 2500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for PEPCID.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

Pregnancy

Pregnancy Category B

Reproductive studies have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively, and in both species at I.V. doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to PEPCID. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from PEPCID, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Patients <1 year of age

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.

Two pharmacokinetic studies in pediatric patients <1 year of age (N=48) demonstrated that clearance of famotidine in patients >3 months to 1 year of age is similar to that seen in older pediatric patients (1-15 years of age) and adults. In contrast, pediatric patients 0-3 months of age had famotidine clearance values that were 2- to 4-fold less than those in older pediatric patients and adults. These studies also show that the mean bioavailability in pediatric patients <1 year of age after oral dosing is similar to older pediatric patients and adults. Pharmacodynamic data in pediatric patients 0-3 months of age suggest that the duration of acid suppression is longer compared with older pediatric patients, consistent with the longer famotidine half-life in pediatric patients 0-3 months of age. (See CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, *Pharmacokinetics* and *Pharmacodynamics*.)

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). Although an intravenous famotidine formulation was available, no patients were

treated with intravenous famotidine in this study. Also, caregivers were instructed to provide conservative treatment including thickened feedings. Enrolled patients were diagnosed primarily by history of vomiting (spitting up) and irritability (fussiness). 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. 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*).

These studies suggest that a starting dose of 0.5 mg/kg/dose of famotidine oral suspension may be of benefit for the treatment of GERD for up to 4 weeks once daily in patients <3 months of age and twice daily in patients 3 months to <1 year of age; the safety and benefit of famotidine treatment beyond 4 weeks have not been established. Famotidine should be considered for the treatment of GERD only if conservative measures (e.g., thickened feedings) are used concurrently and if the potential benefit outweighs the risk.

Pediatric Patients 1-16 years of age

Use of PEPCID in pediatric patients 1-16 years of age is supported by evidence from adequate and well-controlled studies of PEPCID in adults, and by the following studies in pediatric patients: In published studies in small numbers of pediatric patients 1-15 years of age, clearance of famotidine was similar to that seen in adults. In pediatric patients 11-15 years of age, oral doses of 0.5 mg/kg were associated with a mean area under the curve (AUC) similar to that seen in adults treated orally with 40 mg. Similarly, in pediatric patients 1-15 years of age, intravenous doses of 0.5 mg/kg were associated with a mean AUC similar to that seen in adults treated intravenously with 40 mg. Limited published studies also suggest that the relationship between serum concentration and acid suppression is similar in pediatric patients 1-15 years of age as compared with adults. These studies suggest a starting dose for pediatric patients 1-16 years of age as follows:

Peptic ulcer - 0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations - 1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients have employed doses up to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

Geriatric Use

Of the 4,966 subjects in clinical studies who were treated with famotidine, 488 subjects (9.8%) were 65 and older, and 88 subjects (1.7%) were greater than 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, greater sensitivity of some older individuals cannot be ruled out.

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY IN ADULTS, *Pharmacokinetics*). This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of moderate or severe renal impairment is necessary (see PRECAUTIONS, *Patients with Moderate or Severe Renal Insufficiency* and DOSAGE AND ADMINISTRATION, *Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency*).

ADVERSE REACTIONS

The adverse reactions listed below have been reported during domestic and international clinical trials in approximately 2500 patients. In those controlled clinical trials in which PEPCID Tablets were compared to placebo, the incidence of adverse experiences in the group which received PEPCID Tablets, 40 mg at bedtime, was similar to that in the placebo group.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with PEPCID in controlled clinical trials, and may be causally related to the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with PEPCID has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: arrhythmia, AV block, palpitation

Gastrointestinal: cholestatic jaundice, liver enzyme abnormalities, vomiting, nausea, abdominal discomfort, anorexia, dry mouth

Hematologic: rare cases of agranulocytosis, pancytopenia, leukopenia, thrombocytopenia

Hypersensitivity: anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection

Musculoskeletal: musculoskeletal pain including muscle cramps, arthralgia

Nervous System/Psychiatric: grand mal seizure; psychic disturbances, which were reversible in cases for which follow-up was obtained, including hallucinations, confusion, agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence

Respiratory: bronchospasm

Skin: toxic epidermal necrolysis (very rare), alopecia, acne, pruritus, dry skin, flushing

Special Senses: tinnitus, taste disorder

Other: rare cases of impotence and rare cases of gynecomastia have been reported; however, in controlled clinical trials, the incidences were not greater than those seen with placebo.

The adverse reactions reported for PEPCID Tablets may also occur with PEPCID for Oral Suspension and PEPCID RPD Orally Disintegrating Tablets.

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.

OVERDOSAGE

There is no experience to date with deliberate overdosage. Oral doses of up to 640 mg/day have been given to adult patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

The oral LD₅₀ of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 2000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and growth depression in rabbits starting with 200 mg/kg/day orally. The intravenous LD₅₀ of famotidine for mice and rats ranged from 254-563 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

Acute Therapy: The recommended adult oral dosage for active duodenal ulcer is 40 mg once a day at bedtime. Most patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. A regimen of 20 mg b.i.d. is also effective.

Maintenance Therapy: The recommended adult oral dose is 20 mg once a day at bedtime.

Benign Gastric Ulcer

Acute Therapy: The recommended adult oral dosage for active benign gastric ulcer is 40 mg once a day at bedtime.

Gastroesophageal Reflux Disease (GERD)

The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and

ulcerations and accompanying symptoms due to GERD is 20 or 40 mg b.i.d. for up to 12 weeks (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

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). The use of intravenous famotidine in pediatric patients <1 year of age with GERD has not been adequately studied.

Dosage for Pediatric Patients 1-16 years of age

See PRECAUTIONS, *Pediatric Patients 1-16 years of age*.

The studies described in PRECAUTIONS, *Pediatric Patients 1-16 years of age* suggest the following starting doses in pediatric patients 1-16 years of age:

Peptic ulcer - 0.5 mg/kg/day p.o. at bedtime or divided b.i.d. up to 40 mg/day.

Gastroesophageal Reflux Disease with or without esophagitis including erosions and ulcerations - 1.0 mg/kg/day p.o. divided b.i.d. up to 40 mg b.i.d.

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients 1-16 years of age have employed doses up to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

The dosage of PEPCID in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q 6 h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 160 mg q 6 h have been administered to some adult patients with severe Zollinger-Ellison Syndrome.

Oral Suspension

PEPCID for Oral Suspension may be substituted for PEPCID Tablets in any of the above indications. Each five mL contains 40 mg of famotidine after constitution of the powder with 46 mL of Purified Water as directed.

Directions for Preparing PEPCID for Oral Suspension

Prepare suspension at time of dispensing. Slowly add 46 mL of Purified Water. Shake vigorously for 5-10 seconds immediately after adding the water and immediately before use.

Stability of PEPCID for Oral Suspension

Unused constituted oral suspension should be discarded after 30 days.

Orally Disintegrating Tablets

PEPCID RPD Orally Disintegrating Tablets may be substituted for PEPCID Tablets in any of the above indications at the same recommended dosages.

PEPCID RPD Orally Disintegrating Tablets rapidly disintegrate on the tongue. No water is needed for taking the tablet. Patients should be instructed to open the tablet blister pack with dry hands, place the tablet on the tongue to disintegrate and be swallowed with saliva.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency

In adult patients with moderate (creatinine clearance <50 mL/min) or severe (creatinine clearance <10 mL/min) renal insufficiency, the elimination half-life of PEPCID is increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of PEPCID may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

Based on the comparison of pharmacokinetic parameters for PEPCID in adults and pediatric patients, dosage adjustment in pediatric patients with moderate or severe renal insufficiency should be considered.

NDA 19-462/S-030

NDA 19-527/S-024

NDA 20-752/S-005

Page 12

HOW SUPPLIED

No. 3535 — PEPCID Tablets, 20 mg, are beige colored, U-shaped, film-coated tablets coded MSD 963 on one side and PEPCID on the other. They are supplied as follows:

NDC 0006-0963-31 unit of use bottles of 30

NDC 0006-0963-94 unit of use bottles of 90

NDC 0006-0963-58 unit of use bottles of 100

NDC 0006-0963-28 unit dose package of 100

NDC 0006-0963-82 bottles of 1,000

NDC 0006-0963-87 bottles of 10,000

NDC 0006-0963-72 carton of 25 UNIBLISTER™ cards of 31 tablets each.

No. 3536 — PEPCID Tablets, 40 mg, are light brownish-orange, U-shaped, film-coated tablets coded MSD 964 on one side and PEPCID on the other. They are supplied as follows:

NDC 0006-0964-31 unit of use bottles of 30

NDC 0006-0964-94 unit of use bottles of 90

NDC 0006-0964-58 unit of use bottles of 100

NDC 0006-0964-28 unit dose package of 100

NDC 0006-0964-82 bottles of 1,000

NDC 0006-0964-87 bottles of 10,000

NDC 0006-0964-72 carton of 25 UNIBLISTER™ cards of 31 tablets each.

No. 3553 — PEPCID RPD Orally Disintegrating Tablets, 20 mg, are pale rose colored, hexagonal-shaped, lyophilized tablets measuring 13.1 mm (side to side) and 15.2 mm (point to point), with a mint flavor. They are supplied as follows:

NDC 0006-3553-31 unit dose package of 30

NDC 0006-3553-48 unit dose package of 100

NDC 0006-3553-28 unit dose package of 100.

No. 3554 — PEPCID RPD Orally Disintegrating Tablets, 40 mg, are pale rose colored, hexagonal-shaped, lyophilized tablets measuring 15.9 mm (side to side) and 18.4 mm (point to point), with a mint flavor. They are supplied as follows:

NDC 0006-3554-31 unit dose package of 30

NDC 0006-3554-48 unit dose package of 100.

No. 3538 — PEPCID for Oral Suspension is a white to off-white powder containing 400 mg of famotidine for constitution. When constituted as directed, PEPCID for Oral Suspension is a smooth, mobile, off-white, homogeneous suspension with a cherry-banana-mint flavor, containing 40 mg of famotidine per 5 mL.

NDC 0006-3538-92, bottles containing 400 mg famotidine.

Storage

Store PEPCID Tablets and PEPCID RPD Orally Disintegrating Tablets at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

Store PEPCID for Oral Suspension dry powder and suspension at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Suspension: Protect from freezing. Discard unused suspension after 30 days.

PEPCID (famotidine) Tablets and PEPCID (famotidine) for Oral Suspension are manufactured by:

 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

PEPCID RPD (famotidine) Orally Disintegrating Tablets are manufactured for:

 **MERCK & CO., INC.**, Whitehouse Station, NJ 08889, USA

By:

Scherer DDS, Swindon, England and are
Made in England

NDA 19-462/S-030
NDA 19-527/S-024
NDA 20-752/S-005
Page 13

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-462/S-030

19-527/S-024

20-752/S-005

MEDICAL REVIEW(S)

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Medical Officer's Review

Date: April 16, 2002

APPLICATIONS:

NDA 19-462/S-030 Pepcid™ (famotidine) Tablets
NDA 19-527/S-024 Pepcid™ (famotidine) for Oral Suspension
NDA 20-752/S-005 Pepcid RPD™ (famotidine)
Orally Disintegrating Tablets

Material Reviewed: Labeling Revisions based on clinical studies in infants conducted
in accordance with the Agency's written Request

Sponsor: Merck & Co.

Reviewer: Scheldon Kress, M.D. Medical Officer

Introduction

These supplemental NDAs provide Labeling Revisions based on clinical studies in infants conducted in accordance with the Agency's Written Request. Recommendations for labeling revisions were provided in the Medical Officer's Review dated June 25, 2001. In the approvable letters of June 28, 2001, requests for specific additional labeling changes for each of the above referenced drugs were provided.

These applications include study reports that were provided in support of a six-month extension to patent protection for famotidine. Information was provided regarding bioavailability, formulations used in the studies, and safety of famotidine use in infants.

Within these labeling supplemental submissions, the Sponsor provided changes to the proposed Labeling text and package circular as requested by the Agency.

Recommendations For Regulatory Action

For the following Supplemental NDA applications:

NDA 19-462/S-030 Pepcid™ (famotidine) Tablets
NDA 19-527/S-024 Pepcid™ (famotidine) for Oral Suspension
NDA 20-752/S-005 Pepcid RPD™ (famotidine)
Orally Disintegrating Tablets

The recommended revisions specified in the approvable letters of June 28, 2001 have been satisfactorily implemented to the following sections of currently approved labeling:

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS,
PRECAUTIONS,
DOSAGE AND ADMINISTRATION, and
ADVERSE REACTIONS.

I have completed the review of these applications, and they are acceptable

Scheldon Kress, M.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Scheldon Kress
5/3/02 03:34:12 PM
MEDICAL OFFICER

Hugo Gallo Torres
5/3/02 05:25:13 PM
MEDICAL OFFICER

**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

Date submitted: August 28, 2000

Date received: August 28, 2000

Date assigned: February 1, 2001

Review completed: June 25, 2001

Reviewer: Kathy M. Robie-Suh, M.D., Ph.D.

TABLE OF CONTENTS

Cover Page.....	1
Table of Contents.....	2
Table of Abbreviations.....	3
Executive Summary.....	4
<u>Clinical Review</u>	6
Background and Rationale.....	6
Materials Submitted and Reviewed.....	8
Clinical Studies:.....	7
I. Protocol 131.....	7
II. Protocol 129.....	21
III. Protocol 130.....	27
IV. Protocol 136.....	27
Safety Summary.....	29
Proposed Labeling Changes.....	31
Conclusions and Recommendations.....	36
Appendix.....	37

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

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: |
| _____ |
| _____ |
| _____ |
2. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS**, delete the new sub-section titled: | _____ |
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*

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 gastroesophageal 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 patients 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 H₂-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 to 16 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 to 1 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.

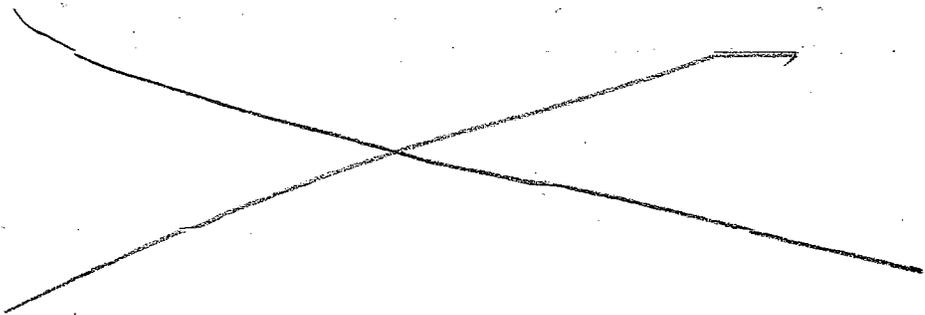
Clinical Studies:

I. Protocol 131: Multicenter Study: A Randomized Placebo-Controlled Evaluation of Oral or I.V. Famotidine in the Treatment of Infants with Gastroesophageal 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.



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

Schedule of Clinical Observations and Laboratory Measurements

Clinic Visit I.D.:	Treatment Weeks									
	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



- 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	36 to 46		37 to 50		36 to 50	
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

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 patients 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 1.0mg			
		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:		4	4		8
Clinical adverse event		2	4		6
Withdrew consent		2	0		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
Completed the phase		1	2	3	2
Switched to marketed formulation		2	2	1	3
Discontinued during the phase:		2	4	2	2
Clinical adverse experience		0	1	0	0
Lost to follow-up		1	0	0	0
Therapy ineffective		1	3	2	2

^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.

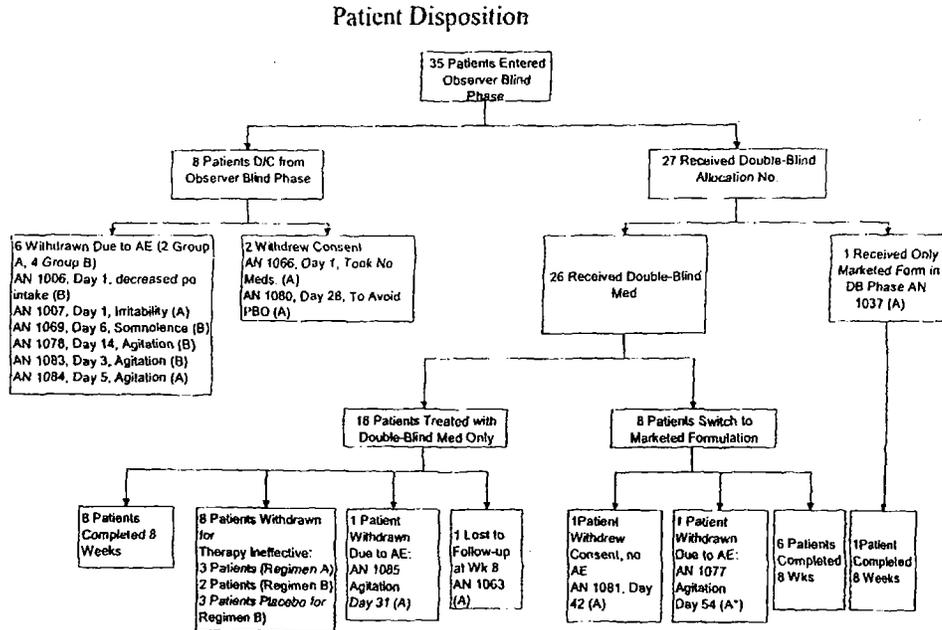


Figure 5 – This figure summarizes patient discontinuation. Patients withdrawn due to adverse experiences of agitation, somnolence, or ineffective therapy (lack of efficacy) are identified by allocation number. The regimen being taken at the time of discontinuation is also noted. A=famotidine-0.5 mg/kg/dose; 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:

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

	Week	Fam 0.5 mg (N=16) [†]			Fam 1.0 mg (N=16) [†]		
		N _i	Measure Mean (std)	Change Mean (std)	N _i	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_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]

Table 32

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

	Week	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) [†]		
		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) [†]			Fam 1.0 mg (N=17) [†]		
	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.
[†] 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) Number (%) of patients:	Fam 0.5 mg (N=18) [†]		Fam 1.0 mg (N=17) [†]	
	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) Number (%) of patients:	Fam 0.5 mg (N=7) [†]		Fam 1.0 mg (N=8) [†]		Placebo 0.5 mg (N=3) [†]		Placebo 1.0 mg (N=8) [†]	
	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)

[†]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 particularly 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-∞} (ng•hr/mL)	609 (384, 967)	576 (525, 632)	1.06 (0.67, 1.67)	>0.25	- [‡]
C _{max} (ng/mL)	79.2 (64.0, 98.1)	97.3 (83.7, 113.2)	0.81 (0.63, 1.06)	0.111	0.037
T _{max} (hr) [§]	2.0 (1.0, 4.1) [¶]	2.3 (2.1, 2.9) [*]	-0.2 (-1.2, 1.9)	0.200	
Half-life (hr)	5.82 (4.64, 7.29)	2.13 (1.78, 2.55)	2.73 (2.05, 3.64)	<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 Dose¹

	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)
Cl _r (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 _{diss} (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-∞} (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 _{12hr} (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 _{24hr} (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

¹ 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.
² 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:

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:

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.

Least Squares Geometric Mean (95% Confidence Intervals) AUC_{0-τ}[†] (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_{0-24 hr} for infants dosed q24h; AUC_{0-12 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 _{0-12 hr}		AUC _{0-24 hr}		Percentage of Time pH		Number of Hours pH	
						[H ⁺] (mM*hr)	pH (pH*hr)	[H ⁺] (mM*hr)	pH (pH*hr)	>4	>3 [‡]	>4	>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]

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
Cl _r (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
V _{dss} (L/kg)	1.29 (1.02, 1.62)	1.53 (1.11, 2.10)	0.84 (0.58, 1.23)	>0.25	— [§]
F _{e1} (%)	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 :

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 _____"

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

Outcome	Number of patients (%)			
	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".

**APPEARS THIS WAY
ON ORIGINAL**

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 _d) (L/kg)	Elimination Half-life (T _{1/2}) (hours)
0-1 months ^b (N=10)	107	0.17 ± 0.06	1.4 ± 0.4	10.9 ± 5.4
0-3 months ^c (N=3)	2886 ± 647	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) ^e	1089 ± 834	0.54 ± 0.34	2.07 ± 1.49	3.38 ± 2.80
11-15 yrs (N=6)	1140 ± 323	0.48 ± 0.14	1.5 ± 0.4	2.3 ± 0.4
Adult (N=16)	1728 ^b	0.59 ± 0.14	1.3 ± 0.2	2.83 ± 0.99

^aValues are presented as means ± SD unless indicated otherwise.
^bMean value only.
^cSingle center study.
^dMulticenter 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, 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 t_{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 $F_{50\%}$ model

	$F_{50\%}$ (ng/mL)
Pediatric Patients	28 ± 12
Data from one study	
a) healthy adult subjects	26.5 ± 10.3
b) adult patients with upper GI bleeding	18.7 ± 10.8

^a Serum concentration of famotidine associated with 50% maximum gastric acid reduction. Values are presented as mean ± SD.

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) ^b	11 (5-19 days)
0.3 mg/kg, single dose	I.V.	gastric pH >3.5 for 8.7 ± 4.7 ^b hours	6 (2-7 years)
0.4-0.8 mg/kg	I.V.	gastric pH >4 for 6-9 hours	18 (2-69 months)
0.5 mg/kg, single dose	I.V.	a >2 pH unit increase above baseline in gastric pH for >3 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 (1-15 years)

^a Values reported in published literature.
^b Mean ± 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

This longer duration of gastric acid suppression is consistent with the decreased clearance in pediatric patients <3 months of age (see Table 6).

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.

PRECAUTIONS.

4. *Proposed:*

PRECAUTIONS

Pediatric Patients <1 year of age

Two pharmacokinetic studies in pediatric patients <1 year of age (N=48) demonstrated that clearance of famotidine in patients >3 months to 1 year of age is similar to that seen in older pediatric patients (1 to 15 years of age) and adults. In contrast, pediatric patients 0-3 months of age had famotidine clearance values that were 2- to 4-fold less than those in older pediatric patients and adults. These studies also show that the mean bioavailability in pediatric patients <1 year of age after oral dosing is similar to older pediatric patients and adults. Pharmacodynamic data in pediatric patients 0-3 months of age suggest that the duration of acid suppression is longer compared with older pediatric patients, consistent with the longer famotidine half-life in pediatric patients 0-3 months of age. (See CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, *Pharmacokinetics and Pharmacodynamics*.)

The famotidine dosing regimen was once daily for patients <3 months of age and twice daily for patients ≥3 months of age.

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*).

These studies suggest that a starting dose of 0.5 mg/kg/dose of famotidine oral suspension may be of benefit for the treatment of GERD for up to 4 weeks once daily in patients <3 months of age and twice daily in patients 3 months to <1 year of age;

Famotidine should be considered for the treatment of GERD only if conservative measures (e.g., thickened feedings) are used concurrently and if the potential benefit outweighs the risk.

*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."

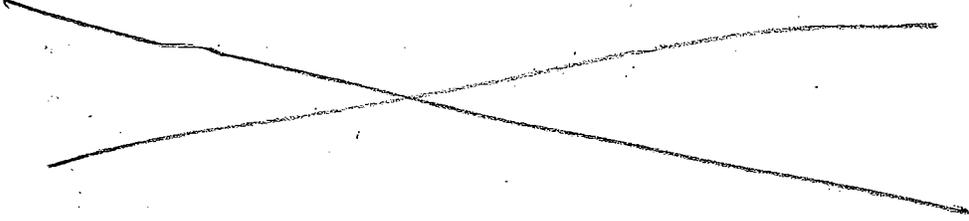
The second paragraph should be deleted and replaced by the following paragraph:

In the last paragraph, the second part of the first sentence should be revised to read: "the safety and benefit of famotidine treatment beyond 4 weeks have not been established."

5. Proposed:

DOSAGE AND ADMINISTRATION

Dosage for Pediatric Patients <1 year of age Gastroesophageal Reflux Disease (GERD)



Reviewer's comment: This paragraph should be deleted and replaced by 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)."*

6. *Proposed:*

In the **ADVERSE REACTIONS** section a Pediatric Patients sub-section is added as follows:

Pediatric Patients. In a clinical study in _____

Reviewer's comment: This sentence should be revised as follows: "Pediatric Patients. In a clinical study in 35 pediatric patients <1 year of age with GERD symptoms (e.g., vomiting (spitting up), _____ (fussing)), agitation was observed in 5 patients on famotidine that resolved when the medication was discontinued."

7. *Proposed:*

The sponsor proposes a few minor editorial changes to the labeling and the following additional changes to the labeling:

- Changes in some section titles to distinguish between pediatric patients <1 year of age and pediatric patients 1-16 years of age.
- In the **PRECAUTIONS**, Pediatric patients 1-16 year of age sub-section the statement regarding _____

Reviewer's comment: These changes are acceptable.

8. *Proposed:*

The text of the labeling changes proposed for the oral formulations and the injectable formulations is identical.

*Reviewer's comment: The sponsor should include in the **DOSAGE AND ADMINISTRATION***

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-180/Division 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

-129-

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
		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]

Attachment
2

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

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

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

Hugo Gallo Torres
6/27/01 04:07:12 PM
MEDICAL OFFICER

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

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-462/S-030

19-527/S-024

20-752/S-005

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW		1. Organization: HFD-180	2. NDA Number: 19-462	
3. Name and Address of Applicant (City & State): Merck & Co., Inc. P.O. Box 4, BLA-20 West Point PA 19486-0004			4. AF Number:	
			Supplement(s)	
6. Name of Drug: Pepcid ®	7. Nonproprietary Name: Famotidine	Number(s) SE8-030	Date(s)	
8. Supplement Provides for: information regarding the bioavailability of the investigational famotidine oral formulations used in these studies. Additional information on the safety of famotidine is provided as well as CMC information.			9. Amendments and Other (Reports, etc.) Dates: None	
10. Pharmacological Category: H ₂ receptor antagonist	11. How Dispensed: Rx	12. Related IND/NDA/DMF(s): NDA 19-462, NDA19-527, IND 18,888		
13. Dosage Form: Oral suspension	14. Potency 1 mg/ml ; 5 mg/ml			
15. Chemical Name and Structure: See NDA 19-462		16. Records and reports.		
		Current Yes <input type="checkbox"/> No <input type="checkbox"/>		
		Reviewed Yes <input type="checkbox"/> No <input type="checkbox"/>		
17. Comments: The pediatric formulation that will be used is the 1 famotidine Oral Suspension (marketed formulation). The manufacturers and packagers have not been changed and the specifications and methods are the same as those found in the approved NDA 19-527. The request of the company for a Categorical Exclusion for the requirements to prepare an Environmental Assessment under 21CFR 25.31(b) seems appropriate based on the data provided. SEE Review Comments for additional information cc: NDA 119-462 HFD-180/Div File HFD-181/PLevine HFD-180/LTalarico HFD-180/MYsem R/D init by: LZhou typist: /MY/ c:/word/supp/19462SE030.1mydoc				
18. Conclusions and Recommendations: From the point of view of CMC this supplement can be approved.				
19. Reviewer				
Name:		Signature		Date Completed: June 18, 2001

1 Page(s) Withheld

552(b)(4) Trade Secret/Confidential

552(b)(5) Deliberative Process

552(b)(5) Draft Labeling

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Maria Ysern
6/25/01 03:28:49 PM
CHEMIST

Marie Kowblansky
6/25/01 04:30:39 PM
CHEMIST
Acting Team Leader for Liang Zhou

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-462/S-030

19-527/S-024

20-752/S-005

**CLINICAL
PHARMACOLOGY/BIOPHARMACEUTICS
REVIEW**

Clinical Pharmacology and Biopharmaceutics Review

NDA: 19-462/SE8-030

Submission Date: August 28, 2000

Name: Pepcid® (Famotidine) tablets, oral suspension and injection

Sponsor: Merck & Co., Inc., West Point, PA 19486

Type of Submission: Supplemental NDA

Reviewer: Shinja R. Kim, Ph.D.

Background: Famotidine is an H₂-receptor antagonist, currently approved to treat peptic ulcer disease, hypersecretory syndromes, and gastroesophageal reflux disease (GERD) in adults and children 1 to 16 years of age. This supplemental NDA is submitted for an approval of uses this drug in infants 0 to 12 months of age. The studies were performed in accordance with a Written Request from the Agency that was issued on 21-Dec-1999 and amended on 08-Jun-2000.

Based on the study results, the sponsor proposed revisions to labeling, and they are provided in Attachment I along with this reviewer's comment.

Overall summary of PK studies: (1) Plasma clearance (Cl_T) was reduced and elimination half-life was prolonged in pediatric patients 0-3 months age compared to older pediatric patients; Cl_T and t_{1/2} for 0-1 month, 0-3 months and >3-12 months ages were found to be 0.13 ± 0.06 L/hr/kg and 10.5 ± 5.4 hrs, 0.21 ± 0.06 L/hr/kg and 8.1 ± 3.5 hrs, 0.49 ± 0.17 L/hr/kg and 4.5 ± 1.1 hrs, respectively. On the other hand, clearance in pediatric patients >3 months-1 year of age was similar to that seen in older pediatric patients (1-15 years old). (2) The duration of effect of famotidine on gastric pH and acid suppression appeared to be longer in younger pediatric patients (e.g., <1 month of age) than in older pediatric patients, and suggests that this effect was due to the decreased clearance in these pediatric patients. (3) The mean bioavailability in pediatric patients <1 year of age was 0.42 which was similar to older pediatric patients and adults. Detailed study results are provided in Attachment II.

Comment: The proposed modification in labeling by the sponsor appears to be adequate per CPB standpoint, except the statement of '_____ (see pages 2-3, modified labeling and the comment). In addition, the sponsor successfully completed pediatric studies in <1 year old patients in accordance with (amended) Written Request from the Agency that was issued on 08-Jun-2000, with respect to CPB related issues.

Recommendation:

This submission is acceptable from the Clinical Pharmacology and Biopharmaceutics perspective provided that the sponsor agrees to the labeling change proposed (pages 2-3) by the Agency. Please forward the recommended modified labeling to the sponsor.

Shinja R. Kim, Ph.D.,
Division of Pharmaceutical Evaluation II

Suresh Doddapaneni, Ph.D., Team Leader

cc: NDA (19-462), HFD-180 (Division File, Levine), HFD-870 (KimSh, DoddapaneniS, MalinowskiH), CDR (Zom Zadeng)

Attachment I

The sponsor revised labeling (underlined) are shown below (limited to CPB related changes) followed by this reviewer's comment where needed:

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).

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 (Vd) (L/kg)	Elimination Half-life (T _{1/2}) (hours)
<u>0-1 month^c (N=10)</u>	NA	<u>0.13 ± 0.06</u>	<u>1.4 ± 0.4</u>	<u>10.5 ± 5.4</u>
<u>0-3 months^d (N=6)</u>	<u>2688 ± 847</u>	<u>0.21 ± 0.06</u>	<u>1.8 ± 0.3</u>	<u>8.1 ± 3.5</u>
<u>>3-12 months^d (N=11)</u>	<u>1160 ± 474</u>	<u>0.49 ± 0.17</u>	<u>2.3 ± 0.7</u>	<u>4.5 ± 1.1</u>
1-11 yrs (N=20)	1089 ± 834	0.54 ± 0.34	2.07 ± 1.49	3.38 ± 2.60
11-15 yrs (N=6)	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

^aValues are presented as means ± SD unless indicated otherwise.

^bMean value only.

^cSingle center study.

^dMulticenter 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 → 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.

~~(---)~~ 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: ~~-----~~

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	6 (2-7 years)
0.4-0.8 mg/kg	I.V.	gastric pH >4 for 6-9 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)

^avalues reported in published literature.

^bMeans ± SD.

^cMean (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.

~~_____~~
 —This longer duration of gastric acid suppression is consistent with the decreased clearance in pediatric patients <3 months of age (see Table 6).

Comment: The study result (Protocol 129) for 0-3 months of age patients does not support, as per the sponsor claims, therefore, the statement is crossed out (i.e., should be deleted). Other sentences can be rearranged as shown above.

PRECAUTIONS

Pediatric Patients <1 year of age

Two pharmacokinetic studies in pediatric patients <1 year of age (N=48) demonstrated that clearance of famotidine in patients >3 months to 1 year of age is similar to that seen in older pediatric patients (1 - 15 years of age) and adults. In contrast, pediatric patients 0-3 months of age had famotidine clearance values that were 2- to 4-fold less than those in older pediatric patients and adults. These studies also show that the mean bioavailability in pediatric patients <1 year of age after oral dosing is similar to older pediatric patients and adults. Pharmacodynamic data in pediatric patients 0-3 months of age suggest that the duration of acid suppression is longer compared with older pediatric patients, consistent with the longer famotidine half-life in pediatric patients 0-3 months of age. (See CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, Pharmacokinetics and Pharmacodynamics.)

Attachment II

Protocol Title (P130): Relative bioavailability of the famotidine suspension 1 mg/ml and marketed Pepcid 40-mg tablets.

Objective: To assess the relative bioavailability of 40-mg oral famotidine suspension (1 mg/ml) and the 40-mg marketed Pepcid 40-mg tablets.

Study design: Open, randomized, 2-period crossover study in 24 healthy males or nonpregnant females (18-45 years of age) to determine the relative bioavailability of the famotidine oral suspension (1 mg/ml) and the PEPCID tablet. Following the single dose of each formulation, subjects were confined for 48 hours for plasma collection. Each treatment period was separated by at least 7 days and the total duration of the study was about 4 weeks.

Clinical supplies:

Treatment A - PEPCID™ 40-mg (marketed) tablet

Treatment B - Marketed product, PEPCID™ Oral Suspension in a bottle containing 400-mg famotidine powder that was constituted according to the market label and diluted with _____ liquid formulation to make a concentration of 1 mg/ml. _____ was provided by the sponsor in market containers. The drug formulation and clinical lot numbers are listed in the table below:

Product	Potency	C No.	Formulation Number
PEPCID™	40 mg	WP-G459	_____
PEPCID™	40 mg	WP-G459A	_____
PEPCID™ for Oral Suspension	400 mg	WP-G460	_____
Empty _____ /bottle	N/A	WP-460	_____

Data Source: Not applicable

Evaluation Criteria:

PK: Blood samples were drawn at t = 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 9, 12, 16, 24, 36 and 48 hrs post dose to determine famotidine plasma concentration. Plasma AUC₀₋₄₈ (ng•hr/ml), plasma C_{max} (ng/ml), and plasma T_{max} (hours) were derived from plasma samples for each treatment.

Analytical Methodology

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ of _____ ng/mL for plasma (_____).

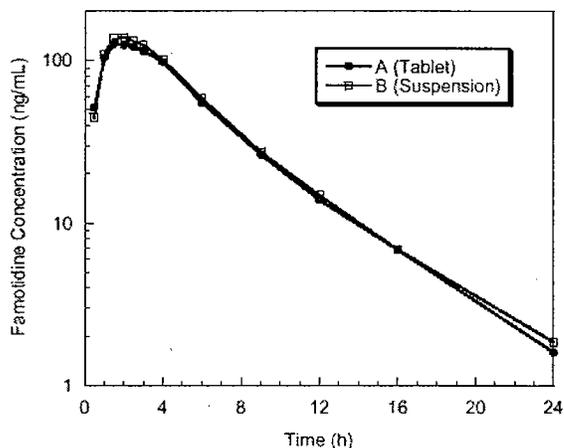
Accuracy and Precision: Between-run accuracy for plasma famotidine ranged from 1.0 to 8.8%, and the precision ranged from 5.7 to 12.2%, respectively.

Data analysis: AUC values were natural log-transformed and analyzed using an ANOVA model appropriate for a 2-period crossover design with factors for treatment, period, subjects within treatment sequence, and treatment sequence. The geometric mean famotidine AUC ratio (suspension/tablet) was estimated by exponentiating the least squares between-treatment difference obtained from the ANOVA. A 95% confidence interval for the between-treatment AUC difference was obtained using the mean square error from the ANOVA and referencing a t-distribution with 22 degrees of freedom. These limits were exponentiated to obtain the 95% confidence interval for the geometric mean AUC ratio. C_{max} was analyzed similarly. T_{max} was

analyzed in exploratory fashion. A distribution-free 95% confidence interval for the median difference (suspension-marketed tablet) was calculated using Hodges-Lehmann estimation.

Results: Mean plasma concentration of famotidine and the summarized PK results are shown in the figure and table below, respectively.

Mean plasma concentration of famotidine following a single dose of PEPCID™ 40-mg tablet or 40-mg famotidine 1 mg/ml suspension (N=24)



Geometric means of PK parameters of famotidine following a single dose of PEPCID™ 40-mg tablet or 40-mg famotidine 1 mg/ml suspension (N=24)

	Tablet (A)	Suspension (B)	Ratio (B/A)	95% CI	p-Value	MSE (log-scale)
AUC _{0-24hr} (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.						

Conclusion: The famotidine 1 mg/ml suspension and the PEPCID™ 40-mg tablet were similar in their bioavailability based on the geometric mean ratios and 95% confidence intervals (suspension/tablet) for the plasma AUC and C_{max} of famotidine (the agency recommends to use 90% CI).

Protocol Title (P129): Pharmacokinetics of Famotidine in Infants Up to 1 Year of Age

Objective(s):

Part I:

Primary: To compare the plasma clearance of famotidine in infants ages 0 to 3 months to that seen historically in older children.

Secondary: (1) To compare the plasma clearance of famotidine in infants ages 0 to 3 months to that seen in infants ages 3 to 12 months. (2) To compare the plasma AUC after administration of famotidine oral suspension in infants ages 0 to 12 months to that seen historically in older children. (3) To assess the relationship between famotidine plasma clearance and age and estimated creatinine clearance. (4) To explore, when possible, the pharmacokinetic-pharmacodynamic relationship for famotidine, following a single intravenous dose of 0.5 mg/kg of famotidine, in patients who require intragastric catheterization for other clinical indications.

Part II:

Primary: To assess the plasma concentration profile following single and repeat doses of famotidine at 2 dose levels in infants ages 0 to 12 months.

Secondary: (1) To evaluate the safety of famotidine following single doses and steady state. (2) To explore the relationship between famotidine plasma AUC and trough plasma concentration and dose after repeat-dose administration. (3) To assess the relationship between famotidine plasma AUC and age and estimated creatinine clearance. (4) To explore, when possible, the pharmacokinetic-pharmacodynamic relationship following single doses and repeat doses (i.e., steady state).

Study Design:

Part I: multicenter, open study in 24 infants. A single intravenous dose of famotidine (0.5 mg/kg) was administered over 2 minutes to infants ages 0 to 3 months (Group I) and ages >3 to 12 months (Group II) and an oral dose of 0.5 mg/kg was given to infants ages 0 to 12 months (Group III).

Part II: multicenter, multiple dosing up to 8 days in 12 infants ages 0 to 12 months. Infants were randomly assigned to receive repeat doses at 1 of 2 possible dose levels.

- Treatment I: 4 infants received 0.25 mg/kg IV single dose (Day 1) followed by 0.25 mg/kg IV on Days 2-8. 2 infants received 0.5 mg/kg P.O. single dose (Day 1) followed by 0.5 mg/kg P.O on Days 2-8.
- Treatment II: 4 infants received 0.25 mg/kg IV on Day 1 and 0.5 mg/kg IV on Days 2 to 8, one infant received 0.5 mg/kg P.O on Day 1 and 0.5 mg/kg IV on Days 2 to 8, and one infant received 0.5 mg/kg P.O on Day 1 and 1 mg/kg P.O on Days 2 to 8.

The dose interval on Days 2 to 8 was once daily for infants ages 0 to 3 months and twice daily for infants >3 months of age.

Clinical supplies:

Product	Trademark Name	Potency	C No.	Formulation No.
Part I				
Famotidine IV	PEPCID™ Injection	10 mg/mL	WP-G009	
Famotidine for oral suspension	PEPCID™ Oral Suspension	400 mg	WP-G010, WP-G010A, WP-G010B	
Part II				
Famotidine for oral suspension	PEPCID™ Oral Suspension	400 mg	WP-G650	
Famotidine injection	PEPCID™ Injection Premixed	20 mg	WP-G653	

Data Source: Not Applicable

Evaluation Criteria:

Part I:

PK: Blood specimens collected at t = -0.25 (predose) and 0.25, 1, 2, 4, 8, 12, 24, and 36 hours post infusion (no 2 & 8 hr blood collections in infants who weighed < 2 kg). Urine samples time intervals: -0.25 to 0 hours, 0-4, 4-8, 8-12, 12-24, 24-36 hr.

PD: Patients in Groups I and II, mean gastric pH was measured at t = -0.25, 0.25, 0.5, 1, 2, 4, 8, 12, 24, 36 hr. Gastric pH was measured by pH probe and by chemstrip.

Part II:

PK: Blood samples following IV dosing at t = -0.25, 0.25, 0.5, 1, 4, 8, 12, 24, and 36 hr postdose (no 8 hr blood collections in infants who weighed <4 kg). Following oral dosing, blood samples were obtained at -0.25 (predose) and 0.5, 1, 2, 4, 8, 12, and 24-hr.

Urine samples time intervals: -0.25-0, 0-4, 4-8, 8-12, 12-24, 24-36 hr.

PD: Gastric pH was measured at t = -0.25, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 hr.

Analytical Methodology

Assay Method: LC/MS/MS

Assay Sensitivity: LOQ of 1 ng/mL using 100 µL plasma and 1 ng/mL using 100 µL urine.

Accuracy and Precision: Between-run accuracy for plasma and urine famotidine ranged from -3 to 2.1%, and -10.7 to 9%, respectively, and the precision ranged from 6.2 to 11.1% and 6 to 11.9%, respectively.

Statistical Analysis:

PK:

Part I: The primary hypothesis (i.e., plasma clearance will be 3-fold less in infants ages 0-3 months than that in older children) was tested by comparing log-transformed plasma clearance following single-dose 0.5 mg/kg IV for infants aged 0 to 3 months and older children using a 2-sample t-test. The secondary hypothesis (plasma clearance will be 3-fold less in infants ages 0-3 months than that in >3-12 months) was tested by comparing log-transformed plasma clearance following 0.5 mg/kg IV for infants aged 0 to 3 months and infants >3 to 12 months of age using an ANOVA model with a factor for age group. Log-transformed AUC following single-oral dose of 0.5 mg/kg was compared for infants aged >3 to 12 months and older children using a 2-sample t-test. When the variances for the 2 groups being compared were significantly different, a 2-sample t-test using unpooled variances with Satterthwaite's approximation.

Part II: Estimates of AUC were obtained using an ANOVA model.

PD: No formal statistical evaluation of pH was performed due to the small number of infants assessed. The time course of pH was graphed for each infant. Change from baseline was calculated for infants at each time point and presented.

Results: 23 and 11 patients were completed for part I and II, respectively.

Part I: Mean plasma concentration of famotidine in infants is shown in Figure 1. PK parameter values for infants (from Part I), older children and adults (from literature data) are listed in Table 1. Table 2 listed PK parameter values for infants aged 0-12 months (Part I, Group III) and older children from literature. Also, plasma clearance is shown in Figure 2 with respect to age.

Figure 1: Mean plasma concentration of famotidine in infants aged 0-3 months and >3-2 months following a Single 0.5-mg/kg IV Dose (left), and in Infants Aged 0-12 Months Following a Single 0.5-mg/kg Oral Dose (right).

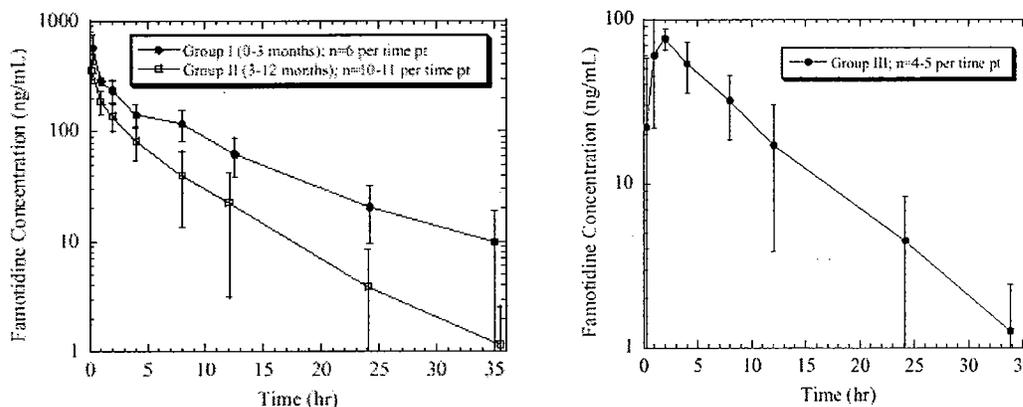


Table 1. Famotidine Pharmacokinetic Parameters in Infants Following a Single 0.5-mg/kg or 0.3 mg/kg IV dose.

	5-19 Days ^a (n = 10)	0-3 Mo Group I (n = 6)	>3-12 Mo Group II (n = 11)	Children 1.1-12.9 Yr ^b (n = 22)	adults 23-32 Yr ^b (n = 16)	Group I vs Group II (p-values)
AUC _{0-∞} (ng*hr/ml)	-	2688 ± 847	1160 ± 474	1089 ± 834	1726 ± 490 ^c	<0.01
CL _p (L/hr/kg)	0.13 ± 0.06	0.21 ± 0.06	0.49 ± 0.17	0.52 ± 0.34	0.39 ± 0.1	<0.01
CL _r (L/hr/kg)	0.09 ± 0.06	0.15 ± 0.04	0.31 ± 0.13	0.43 ± 0.24	0.27 ± 0.1	<0.01
V _d (L/kg)	1.4 ± 0.4	1.8 ± 0.3	2.3 ± 0.7	1.9 ± 1.5	1.3 ± 0.5	0.064
t _{1/2} (hr)	10.5 ± 5.4	8.1 ± 3.5	4.5 ± 1.1	3.3 ± 2.5	2.83 ± 1.0	<0.01

^aProtocol 136

^bLiterature data

^cValue based on extrapolation from a 20 mg (~0.28 mg/kg IV) dose to a 40 mg IV dose.

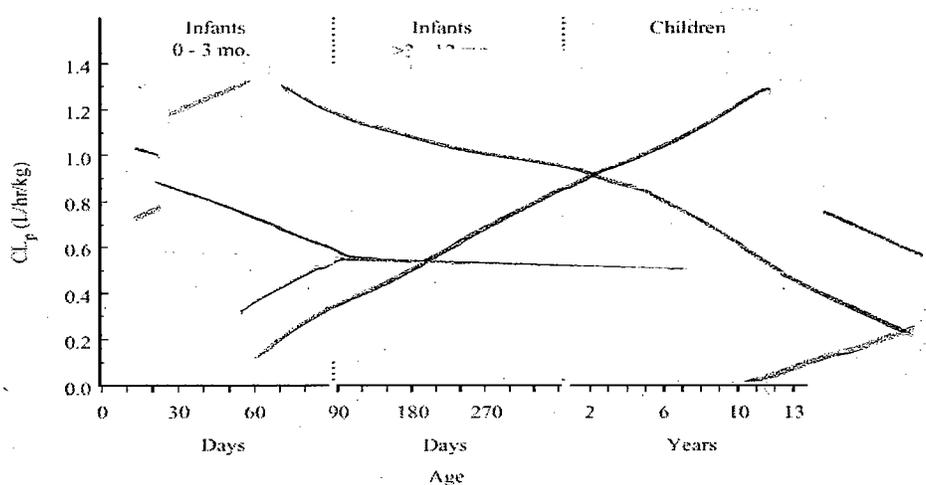
Table 2. Geometric Means (95% Confidence Intervals) of Pharmacokinetic Parameters for Famotidine in Infants Aged 0 to 12 Months and Children Aged 11 to 15 Years Following a Single 0.5-mg/kg Oral Dose of Famotidine.

	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
AUC _{0-∞} (ng•hr/mL)	609 (384, 967)	576 (525, 632)	1.06 (0.67, 1.67)	>0.25
C _{max} (ng/mL)	79.2 (64.0, 98.1)	97.3 (83.7, 113.2)	0.81 (0.63, 1.06)	0.111
T _{max} (hr) [‡]	2.0 (1.0, 4.1) [§]	2.3 (2.1, 2.9)	-0.2 [‡] (-1.2, 1.9)	0.200
Half-life (hr)	5.82 (4.64, 7.29)	2.13 (1.78, 2.55)	2.73 (2.05, 3.64)	<0.01

[‡] 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.

Note: Arithmetic mean ± SD for AUC_{0-∞} for Group III and older children are 645 ± 249 and 579 ± 66 ng•hr/ml, respectively.

Figure 2. Individual Values of Plasma Clearance (L/hr/kg) With Geometric Means (♦) and 95% Confidence Intervals 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^a of Famotidine



^aInfants received 0.5 mg/kg IV; children received either 0.3 mg/kg IV or 0.5 mg/kg IV.

Part II:

Figure 4. Mean plasma concentration profiles (dose- corrected) of famotidine in infants aged 0 to 12 months following single and multiple iv doses.

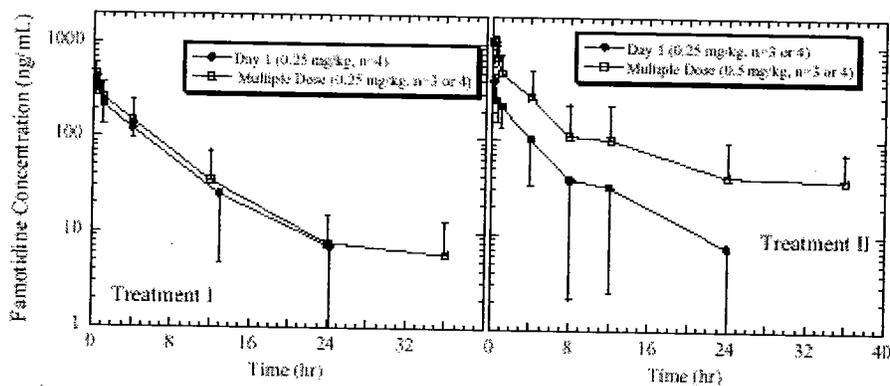


Table 3. Least Squares Geometric Means (95% Confidence Intervals) of AUC (†) for Famotidine in Pediatric Patients Aged 0 to 12 Months Following Single and Multiple Doses of 0.25 mg/kg IV (0.5 mg/kg P.O.) or 0.5 mg/kg IV (1 mg/kg P.O.)

Single or Multiple Dose	Dose (mg/kg)	N	Least Squares Estimate ¹ (95% CI)	Ratio (A/B) (90% CI)	p-Value
Single dose	0.25 IV + 0.5 P.O. (B) ²	12	1134.2 (940.9, 1367.3)	1.40 (1.14, 1.72)	0.010
	0.5 IV (A) ¹	17	1587.1 (1357.6, 1855.4)		
Multiple dose	0.25 IV + 0.5 P.O. (B) ²	6	1190.7 (752.9, 1883.2)	2.68 (1.56, 4.62)	0.012
	0.5 IV + 1.0 P.O. (A) ¹	5	3196.1 (1933.5, 5283.3)		
Single dose (bioavailability estimate)	0.5 IV (B) ³	17	1488.5	0.42 (0.29, 0.60) ⁴	-
	0.5 P.O. (A) ¹	5	622.0		
Multiple dose (accumulation)(A) ¹	0.25 IV - 0.5 PO	6	1266	1.01	-
Single dose (B) ⁵	0.25 IV + 0.5 PO	6	1253	(0.7, 1.47) ⁶	-

¹ AUC_{0-∞} for single-dose comparison and AUC_{0-t} for multiple-dose comparisons.
² For all analyses except accumulation, the ANOVA includes age as a covariate, estimates represent the expected AUC based on the age of all infants included in the analysis.
³ (B) indicates denominator for between-dose comparison.
⁴ (A) indicates numerator for between-dose comparison.
⁵ Ninety-five percent confidence interval.

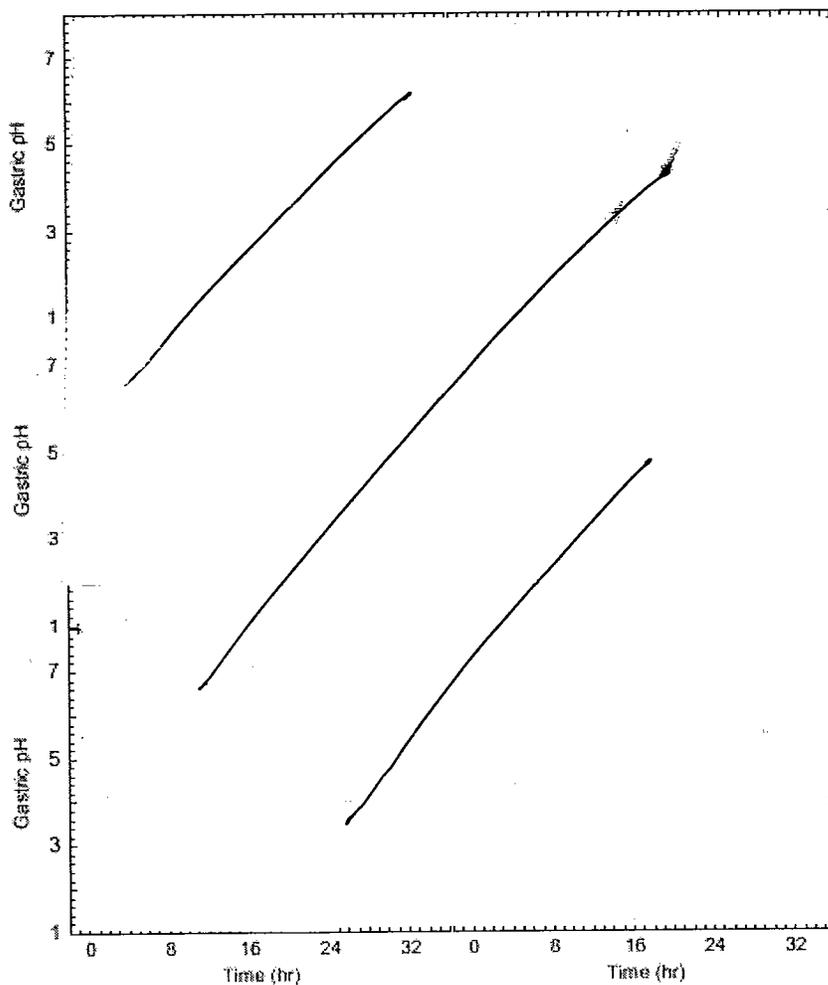
Pharmacodynamics: 6 infants had pH measurements done (part I and II), and the results are presented in Table 5 and Figure 5.

Table 5. Individual Values of Measurements of Gastric pH Over 24 Hours in Infants Aged 0 to 12 Months Following Single and Multiple Doses of Famotidine (results found by the sponsor).

AN	Age (Days)	Day	Dose	Pre-dose pH	pH Monitoring Interval	Percentage of Time pH		Number of Hours pH	
						>4 ¹	≥3 ²	>4	≥3
115	126	1	0.5 mg/kg IV	5.6	0 to 20.23 hr	100 ³	100 ³	20.23	20.23
401	17	1	0.5 mg/kg IV	4.9	0 to 35.9 hr	74.0	82.4	26.56	29.58
3002	58	1	0.25 mg/kg IV	4.9	0 to 4.02 hr	100 ³	100 ³	4.02	4.02
1010	58	1	0.25 mg/kg IV	3.0	0 to 24.08 hr	46.8	89.9	11.26	19.49
1006	30	1	0.25 mg/kg IV	5.5	0 to 24.02 hr	100	100	24.02	24.02
1006	34	4	0.5 mg/kg IV	7.5	0 to 35.97 hr	96.3	100	34.64	35.97

¹ Calculated as (no. of hours pH>4)/(total no. of hours pH monitored)---note that denominator differs from patient to patient.
² Calculated as (no. of hours pH≥3)/(total no. of hours pH monitored)---note that denominator differs from patient to patient.
³ pH monitored for <24 hours.

Figure 5. Individual Gastric pH Profiles for Infants Aged 0 to 12 Months Following Single/Multiple IV Doses of 0.25 mg/kg IV or 0.5 mg/kg Famotidine.



Two infants, AN 401 and 1010, had baseline pH of 4.0 or less. The sponsor claimed that ~~_____~~ However, the data does not support as claims (see Figure 5).

Conclusions:

- Famotidine systemic and renal clearance were reduced and half-life was 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.
- AUC, C_{max} and T_{max} values after oral administration of 0.5 mg/kg in infants were comparable to corresponding values in previously reported studies in children 11-15 years of age, while, half-life was significantly longer in infants aged 0-12 months compared to that in children aged 11-15 years (Table 2). However, it appears that PK parameter values among >3-12 months, 1.1-12.9 years and adults were similar as shown in Table 1.
- Based on between-patient comparisons, AUC was 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.
- There was no evidence of accumulation with the 0.25-mg/kg IV or 0.5-mg/kg P.O. dose based on AUC.
- The systemic bioavailability of famotidine in infants is approximately 42% based on between-patient comparisons after IV and oral dosing.
- The effect of famotidine, measured by gastric pH, appears to be not conclusive.

Protocol Title (P136): Pharmacokinetics and Pharmacodynamics of Famotidine in Infants.

Objectives: (1) Characterization of the PK of famotidine in infants compared to older infants and children. (2) Determination and characterization of the PK-PD relationship for famotidine in patients with a low initial intragastric pH. (3) Use of the PK and PD data to project famotidine dosing regimens in infants.

Study Design: This was an investigator initiated study and was not sponsored by Merck & Co., Inc. Merck & Co., Inc., obtained the primary data from the investigator and provided the analyses in this report in response to the FDA Written Request for pediatric studies for famotidine. This was open-label study in 12 infants 5 to 19 days old. An administered dose was a single intravenous famotidine, 0.5 mg/kg over 15 minutes (used marketed IV formulation of PEPCID) and subjects were observed for 24 hrs.

Evaluation Criteria:

PK: Blood was collected at predose and 0.5, 1, 2, 6, 12, and 24 hours after the end of the infusion for infants weighing =1200 grams. For infants weighing between 800 and 1200 grams, blood was collected at predose and 1, 4, 12, and 24 hours after the end of infusion. Urine was also collected for the following intervals: -2-0 hr (predose) and 0-4, 4-8, 8-12 and 12-24 hrs postdose. The following PK parameters were calculated by analyzing blood and urine samples: plasma clearance (CL), renal clearance (CL_r), half-life (t_{1/2}), volume of distribution (Vd_{ss}), extrapolated concentration at time zero of a bolus dose (C₀), and fraction of dose eliminated unchanged in urine (F_u).

PD: Intragastric pH readings were recorded prior to famotidine administration, every 5 minutes during infusion, 5, 10, 15, 45 minutes and 1, 1.5, 2, 3, 4, 6, 12, 16, and 24 hours after the end of the infusion. These gastric pH data were analyzed by MRL as specified in the FDA Written Request for pediatric studies for famotidine.

Analytical Assay: The sponsor reported that famotidine was analyzed by HPLC-UV, and the method had an LOQ of ~~—~~ µg/mL in plasma and ~~—~~ µg/mL in urine. No accuracy/precision results were submitted.

Statistical analysis:

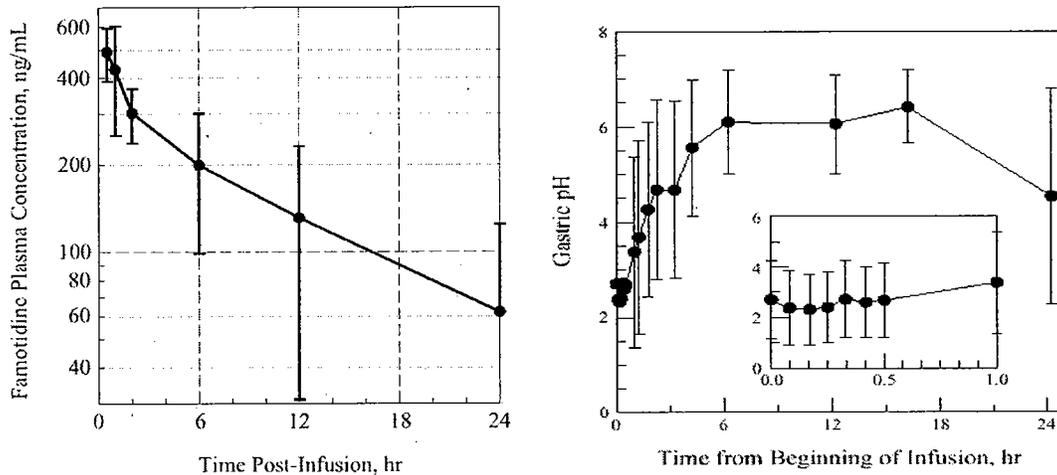
PK parameters were compared between infants aged 5 to 19 days old (neonates) and historical data in older children using natural log-transformed data and evaluated in an ANOVA model having a factor for age (infants, older children).

Summary statistics for pH change from baseline were calculated at each time point using the Wilcoxon rank-sum test. Mean and median percent of time and number of hours pH was above 3 and above 4 were calculated. 95% confidence intervals for mean percent of time and mean number of hours were calculated.

Results 10, 11 and 12 patients completed for PK, PD and safety determination, respectively.

PK and PD: Results are presented in tables and figures.

Mean Famotidine Plasma Concentrations (left panel) and the Mean Gastric pH Over Time (right panel) in Infants Aged 5 to 19 Days Following a Single 15-Minute 0.5 mg/kg IV Dose of Famotidine.



Geometric Means (95% Confidence Intervals) of PK 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
Plasma clearance (L/hr/kg)	0.12 (0.07, 0.18)	0.42 (0.31, 0.56)	0.28 (0.16, 0.48)	<0.01
Renal clearance (L/hr/kg)	0.08 (0.05, 0.11)	0.38 (0.26, 0.55)	0.20 (0.12, 0.35)	<0.01
Elimination half-life (hr)	9.5 (6.5, 14.0)	2.7 (2.0, 3.4)	3.59 (2.25, 5.71)	<0.01
Steady state distribution volume (L/kg)	1.29 (1.02, 1.62)	1.53 (1.11, 2.10)	0.84 (0.58, 1.23)	>0.25
Fraction eliminated in urine (%)	66.3 (52.1, 84.3)	67.6 (53.7, 85.1)	0.98 (0.70, 1.37)	>0.25

[†] 0.5 mg/kg over 15 minutes.
[‡] 0.3 mg/kg bolus or 0.5 mg/kg over 15 minutes.
 Pharmacokinetic data after IV administration of famotidine to adults showed mean (SD) values for plasma clearance of 0.39 (0.14) L/kg/hr, elimination half-life of 2.8 (1) hours, and steady state distribution volume of 1.3 (0.2) L/kg. The range of mean values for renal clearance was 0.16 to 0.27 and for fraction eliminated in urine was 67 to 79%.

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 (n=11)

	Percentage of Time pH		Number of Hours pH	
	>4	>3	>4	>3
Mean	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	13.8	7.8	3.3	1.9
Median	84.2	88.4	20.4	21.4

Previous data showed that a single administration of 20 and 40 mg famotidine in adults inhibited acid secretion for 10 to 12 hours. Historical data suggested that single IV doses of 0.3 and 0.8 mg/kg famotidine increased gastric pH to more than 3.5 for 6 to 9 hours in studies in children ages 2 to 7 years. A single IV dose of 0.5 mg/kg famotidine increased pH for approximately 20 hours postdose in these newborns.

CONCLUSIONS:

- Famotidine systemic and renal clearance were reduced and half-life was prolonged in neonates compared with the corresponding values in previously reported studies in children older than 1 year and adults.
- Administration of 0.5 mg/kg famotidine IV to neonates increased gastric pH to > 4 for a prolonged interval (20 hours), consistent with the prolonged elimination half-life in this population.

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/s/

Shinja Kim
5/24/01 09:54:44 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

19-462/S-030

19-527/S-024

20-752/S-005

**ADMINISTRATIVE AND CORRESPONDENCE
DOCUMENTS**



NDA 19-462
NDA 20-752
NDA 19-527

Merck & Co., Inc.
Attention: Virginia G. Snyder
Manager, Regulatory Affairs
P.O. Box 4, BLA-20
West Point, PA 19486

Dear Ms. Snyder:

We acknowledge receipt of your October 25, 2002, submission on October 28, 2002, containing final printed labeling in response to our June 06, 2002, letter approving the following supplemental new drug applications.

NDA 19-462/S-030 Pepsid™ (famotidine) Tablets,
NDA 20-752/S-005 Pepsid RPD (famotidine) Orally Disintegrating Tablets
NDA 19-527/S-024 Pepsid (famotidine) for Oral Suspension.

We have reviewed the labeling that you submitted in accordance with our June 06, 2002, approval letter and we find it acceptable.

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at 301-827-7310.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal
and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Paul Levine
5/22/03 02:51:36 PM
For Robert Justice, M.D., M.S.; Division Director

Division of Gastrointestinal & Coagulation Drug Products

REGULATORY HEALTH PROJECT MANAGER REVIEW

Material Reviewed

Sponsor: Merck Research Laboratories

Submission Date: October 25, 2002 (Final Printed Labeling)

Receipt Date: October 28, 2002

Application Number	Name of Drug	EDR address
NDA 19-462/SE8-030	Pepcid™ (famotidine) Tablets	
NDA 20-752/SE8-005	Pepcid RPD™ (famotidine) Orally Disintegrating Tablets	
NDA 19-527/SE8-024	Pepcid™ (famotidine) for Oral Suspension	

Background and Summary Description:

Oral Pepcid was approved under NDA 19-462 on October 15, 1986; NDA 19-527 on February 2, 1987; and NDA 20-752 on May 28, 1998; for the following indications:

1. Short term treatment of active duodenal ulcer
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.
3. Short term treatment of active benign gastric ulcer

* Note: The oral formulations share a common PI.

In a letter dated December 22, 1999, the sponsor informed the Agency that it no longer intended to manufacture and sell Pepcid RPD® Disintegrating Tablets. The sponsor stated that it would exhaust existing supplies of Pepcid RPD and would not return the drug to the market until a supplement was submitted to and approved by the FDA.

On August 28, 2000, in response to our August 13, 1999, Written Request as amended on December 20, 1999, the sponsor submitted efficacy supplemental new drug applications in support of pediatric exclusivity for oral and injection products of Pepcid™ (famotidine). These supplements provide for study reports in support of a six-month extension to patent protection

based upon pediatric exclusivity as well as information regarding the bioavailability of famotidine. In addition, the sponsor proposed changes to the following sections of the approved package insert: CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ADVERSE REACTIONS sections.

In a letter dated June 28, 2001, the Agency notified the sponsor that the supplemental new drug applications submitted August 28, 2000, were approvable. The Agency requested that the sponsor submit draft labeling that contained revised text to the CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS, PRECAUTIONS, DOSAGE AND ADMINISTRATION and ADVERSE REACTIONS sections

On August 10, 2001, the sponsor submitted revised labeling as an amendment to the supplemental new drug applications, in response to our approvable letter, dated June 28, 2001.

In a letter dated June 06, 2002, the Agency notified the sponsor that the supplemental new drug applications were approved, and requested that the sponsor submit final printed labeling (FPL) identical to the draft labeling.

On October 25, 2002, the sponsor submitted FPL in response to the approval letter, dated June 06, 2002.

Review

The FPL (package insert) submitted October 25, 2002, identified as "7825036 June 2002", was compared to the currently approved labeling, approved June 06, 2002, and identified as "78235X" March XXXXX 2001".

The FPL (package insert) submitted October 25, 2002, is identical to the package insert in the currently approved labeling except for the following changes. All deletions are indicated by ~~strikethroughs~~ and all additions are indicated by underlines.

1. The following text has been deleted from the title on each page of the package insert.

~~"PEPCID RPD (FAMOTIDINE) ORALLY DISINTEGRATING TABLETS"~~

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD® Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

2. The fourth paragraph under the **DESCRIPTION** section has been deleted as follows:

~~"Each Orally Disintegrating Tablet for oral administration contains either 20 mg or 40 mg of famotidine and the following inactive ingredients: aspartame, mint flavor, gelatin, mannitol, red ferric oxide, and xanthan gum."~~

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

3. The second sentence of the first paragraph under the *Pharmacokinetics* subsection of the **CLINICAL PHARMACOLOGY IN ADULTS** section of the package insert has been revised as follows:

~~"The bioavailability of oral doses is 40-45%. PEPCID Tablets, and PEPCID for Oral Suspension and PEPCID RPD Orally Disintegrating Tablets are bioequivalent."~~

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

4. The second and third paragraphs under the *Information for Patients* subsection of the **PRECAUTIONS** section has been deleted as follows:

~~"Patients should be instructed to leave the PEPCID RPD Orally Disintegrating Tablet in the unopened package until the time of use. Patients should then open the tablet blister pack with dry hands, place the tablet on the tongue to dissolve and be swallowed with saliva. No water is needed for taking the tablet."~~

~~*Phenylketonurics:* Phenylketonuric patients should be informed that PEPCID RPD contains phenylalanine 1.05 mg per 20 mg orally disintegrating tablet and 2.10 mg per 40 mg orally disintegrating tablet."~~

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

5. The first sentence of the fourth paragraph under the *Nursing Mothers* subsection of the **PRECAUTIONS** section has been revised as follows:

"In a double-blind, randomized, treatment-withdrawal study, 35 pediatric patients <1 year of ..."

Comment: This minor editorial revision is acceptable.

6. The first sentence of the second paragraph under the *Other* subsection of the **ADVERSE REACTIONS** section has been revised as follows:

"The adverse reactions reported for PEPCID Tablets may also occur with PEPCID for Oral Suspension and ~~PEPCID RPD Orally Disintegrating Tablets.~~"

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

7. The *Orally Disintegrating Tablets* subsection of the **DOSAGE AND ADMINISTRATION** section has been deleted as follows:

~~Orally Disintegrating Tablets~~

~~PEPCID RPD Orally Disintegrating Tablets may be substituted for PEPCID Tablets in any of the above indications at the same recommended dosages.~~

~~PEPCID RPD Orally Disintegrating Tablets rapidly disintegrate on the tongue. No water is needed for taking the tablet. Patients should be instructed to open the tablet blister pack with dry hands, place the tablet on the tongue to disintegrate and be swallowed with saliva.~~

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

8. Under the **HOW SUPPLIED** section, the following text has been deleted:

No. 3553 — PEPCID RPD Orally Disintegrating Tablets, 20 mg, are pale rose colored, hexagonal-shaped, lyophilized tablets measuring 13.1 mm (side to side) and 15.2 mm (point to point), with a mint flavor. They are supplied as follows:

NDC 0006-3553-31 unit dose package of 30

NDC 0006-3553-48 unit dose package of 100

NDC 0006-3553-28 unit dose package of 100.

No. 3554 — PEPCID RPD Orally Disintegrating Tablets, 40 mg, are pale rose colored, hexagonal-shaped, lyophilized tablets measuring 15.9 mm (side to side) and 18.4 mm (point to point), with a mint flavor. They are supplied as follows:

NDC 0006-3554-31 unit dose package of 30

NDC 0006-3554-48 unit dose package of 100.

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

9. Under the first sentence of the *Storage* subsection of the **HOW SUPPLIED** section, the text has been revised as follows:

“Store PEPCID Tablets and ~~PEPCID RPD Orally Disintegrating Tablets~~ at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].”

Comment: This change is acceptable as it correlates with the sponsor's voluntary decision not to manufacture and sell Pepcid RPD[®] Disintegrating Tablets as indicated in the sponsor's letter, dated December 22, 1999.

Conclusion

1. The approved FPL (package insert) is identified as “7825036 June 2002”.
2. An Acknowledge and Retain letter should be issued for the supplemental new drug applications for Pepcid[™] oral formulations: NDAs 19-462/S-030, 19-527/S-024, and 20-752/S-005.

Drafted: March 25, 2003

Initialed: R. Justice - Mon 4/14/2003 5:00 PM

S. Doddapaneni - Wed 4/16/2003 8:28 AM

Finalized: May 22, 2003

Filename: Review of FPL 19462_S-30 et al sub 102502.doc

CSO LABELING REVIEW

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this page is the manifestation of the electronic signature.**

/s/

Paul Levine
5/22/03 02:38:50 PM
CSO

NDA 19-462/S-030
NDA 19-510/S-028
NDA 19-527/S-024
NDA 20-249/S-011
NDA 20-752/S-005

**PEDIATRIC EXCLUSIVITY
DETERMINATION SUPPLEMENT**

Merck Research Laboratories
Attention: Michelle W. Kloss, Ph.D.
P.O. Box 4, BLA-20
West Point, PA 19486-0004

Dear Dr. Kloss:

We have received your supplemental drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA 19-462/S-030: Pepcid (famotidine) Tablets
NDA 19-510/S-028: Pepcid Injection (famotidine)
NDA 19-527/S-024: Pepcid (famotidine) for Oral Suspension
NDA 20-249/S-011: Pepcid Injection Premixed (famotidine)
NDA 20-752/S-005: Pepcid RPD (famotidine) Orally Disintegrating Tablets

Review Priority Classification: Standard (S)

Date of Supplements: August 28, 2000

Date of Receipt: August 29, 2000

These supplements contain pediatric study reports in support of a six month extension to patent protection based upon pediatric exclusivity. In addition, the supplement contains information regarding the bioavailability of the famotidine oral formulations used in the studies, information concerning safety of famotidine use in infants, and draft package inserts.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b), in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 27, 2000.

Please cite the application number listed above at the top of the first page of any communications concerning these applications. All communications concerning these supplemental applications

NDA 19-462, NDA 19-510, NDA 19-527, NDA 20-249, NDA 20-752

Page 2

should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call Paul E. Levine, Jr., R.Ph., Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Paul E. Levine, Jr., R.Ph.
Regulatory Project manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 19-462, NDA 19-510, NDA 19-527, NDA 20-249, NDA 20-752

Page 3

cc:

Archival NDA 19-462
NDA 19-510
NDA 19-527
NDA 20-249
NDA 20-752
NDA 20-325
NDA 20-801
NDA 20-902

HFD-180/Div. Files
HFD-180/P.Levine
DISTRICT OFFICE

Drafted by: PEL/September 28, 2000
Initialed by: KJ-10/02/00
final: 10/03/00
filename: Pepcid Ped Excl Supp 092100.doc

ACKNOWLEDGEMENT (AC)