CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

19-510/S028
20-249/S011

Trade Name: Pepcid Injection
Pepcid Injection Premixed

Generic Name: (famotidine)

Sponsor: Merck and Company, Inc.

Approval Date: June 28, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-510/S028

20-249/S011

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-510/S028

20-249/S011

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-510/S-028
NDA 20-249/S-011

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 19-510/S-028: Pepcid™ Injection (famotidine)
NDA 20-249/S-011: Pepcid™ Injection Premixed (famotidine)

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.

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
6/6/02 06:57:31 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-510 /S028

20-249/S011

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-510/S-028
NDA 20-249/S-011

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 19-510/S-028: Pepcid Injection (famotidine)
NDA 20-249/S-011: Pepcid Injection Premixed (famotidine)

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.

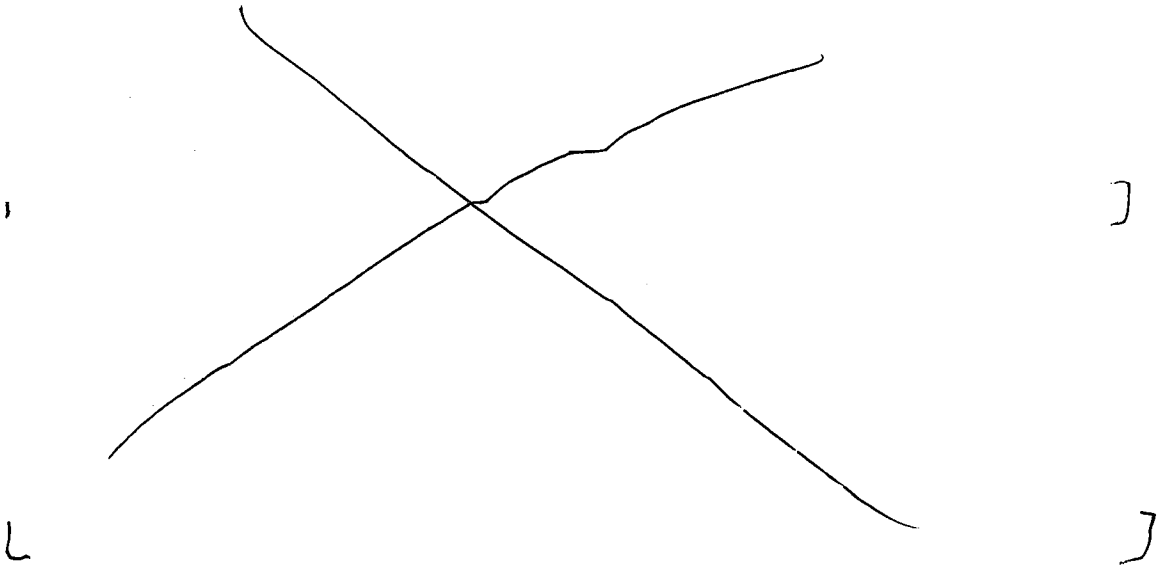
We have completed the review of these applications, and it is approvable. Before these applications may be approved, however, it will be necessary for you to submit draft labeling revised as follows:

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

2. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS,** delete the new

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).



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 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."

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 the use of the parenteral products in pediatric patients <1 year of age.

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 04:39:09 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-510/S028

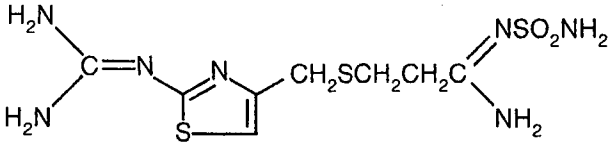
20-249/S011

LABELING

PEPCID®
(FAMOTIDINE) INJECTION PREMIXED
PEPCID®
(FAMOTIDINE) INJECTION

DESCRIPTION

The active ingredient in PEPCID* (famotidine) Injection Premixed and PEPCID (famotidine) Injection is a histamine H_2-receptor antagonist. Famotidine is *N'*-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]propanimidamide. The empirical formula of famotidine is $C_8H_{15}N_7O_2S_3$ 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.

PEPCID Injection Premixed is supplied as a sterile solution, for intravenous use only, in plastic single dose containers. Each 50 mL of the premixed, iso-osmotic intravenous injection contains 20 mg famotidine, USP, and the following inactive ingredients: L-aspartic acid 6.8 mg, sodium chloride, USP, 450 mg, and Water for Injection. The pH ranges from 5.7 to 6.4 and may have been adjusted with additional L-aspartic acid or with sodium hydroxide.

The plastic container is fabricated from a specially designed multilayer plastic (PL 2501). Solutions are in contact with the polyethylene layer of the container and can leach out certain chemical components of the plastic in very small amounts within the expiration period. The suitability and safety of the plastic have been confirmed in tests in animals according to the USP biological tests for plastic containers, as well as by tissue culture toxicity studies.

PEPCID (famotidine) Injection is supplied as a sterile concentrated solution for intravenous injection. Each mL of the solution contains 10 mg of famotidine and the following inactive ingredients: L-aspartic acid 4 mg, mannitol 20 mg, and Water for Injection q.s. 1 mL. The multidose injection also contains benzyl alcohol 0.9% added as preservative.

CLINICAL PHARMACOLOGY IN ADULTS

GI Effects

PEPCID is a competitive inhibitor of histamine H_2-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.

After intravenous administration, the maximum effect was achieved within 30 minutes. Single intravenous doses of 10 and 20 mg inhibited nocturnal secretion for a period of 10 to 12 hours. The 20 mg dose was associated with the longest duration of action in most subjects.

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

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* Registered trademark of MERCK & CO., Inc.

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.

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

Orally administered PEPCID is incompletely absorbed and its bioavailability is 40-45%. 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

The majority of clinical study experience involved oral administration of PEPCID Tablets, and is provided herein for reference.

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≤0.05, p≤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≤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≤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≤0.01 vs Placebo
‡ p≤0.05 vs PEPCID 20 mg b.i.d.
‡‡ p≤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

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

Plasma clearance is reduced and elimination half-life is prolonged in pediatric patients 0-3 months of age compared to older pediatric patients. The pharmacokinetic parameters for pediatric patients, ages >3 months-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

	EC_{50} (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)

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

The duration of effect of famotidine I.V. 0.5 mg/kg on gastric pH and acid suppression was shown in one study to be longer in pediatric patients <1 month of age than in older pediatric patients. 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 Injection Premixed, supplied as a premixed solution in plastic containers (PL 2501 Plastic), and PEPCID Injection, supplied as a concentrated solution for intravenous injection, are intended for intravenous use only. PEPCID Injection Premixed and PEPCID Injection are indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage forms for short term use in patients who are unable to take oral medication for the following conditions:

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 H_2-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, DOSAGE AND ADMINISTRATION).

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 that the starting dose for pediatric patients 1-16 years of age is 0.25 mg/kg intravenously (injected over a period of not less than two minutes or as a 15 minute infusion) q 12 h up to 40 mg/day.

While published uncontrolled clinical studies suggest effectiveness of famotidine in the treatment of 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 gastric pH determination and endoscopy. Published uncontrolled studies in pediatric patients have demonstrated gastric acid suppression with doses up to 0.5 mg/kg intravenously q 12 h.

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 patients 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, PEPCID RPD Orally Disintegrating Tablets, PEPCID Injection Premixed or PEPCID Injection. In addition, transient irritation at the injection site has been observed with PEPCID Injection.

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 intravenous LD_{50} 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. The oral LD_{50} 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.

DOSAGE AND ADMINISTRATION

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, PEPCID Injection Premixed or PEPCID Injection may be administered until oral therapy can be instituted.

The recommended dosage for PEPCID Injection Premixed and PEPCID Injection in adult patients is 20 mg intravenously q 12 h.

The doses and regimen for parenteral administration in patients with GERD have not been established.

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 that the starting dose in pediatric patients 1-16 years of age is 0.25 mg/kg intravenously (injected over a period of not less than two minutes or as a 15 minute infusion) q 12 h up to 40 mg/day.

While published uncontrolled clinical studies suggest effectiveness of famotidine in the treatment of 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 gastric pH determination and endoscopy. Published uncontrolled studies in pediatric patients 1–16 years of age have demonstrated gastric acid suppression with doses up to 0.5 mg/kg intravenously q 12 h.

Dosage Adjustments 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 Injection Premixed or PEPCID Injection 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.

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 intravenous dose is 20 mg q 12 h. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. In some patients, a higher starting dose may be required. Oral doses up to 160 mg q 6 h have been administered to some adult patients with severe Zollinger-Ellison Syndrome.

PEPCID Injection Premixed

PEPCID Injection Premixed, supplied in Galaxy§ containers (PL 2501 Plastic), is a 50 mL iso-osmotic solution premixed with 0.9% sodium chloride for administration as an infusion over a 15-30 minute period. *This premixed solution is for intravenous use only using sterile equipment.*

Directions for Use of Galaxy® Containers

Check the container for minute leaks prior to use by squeezing the bag firmly. If leaks are found, discard solution as sterility may be impaired. Do not add supplementary medication. Do not use unless solution is clear and seal is intact.

CAUTION: Do not use plastic containers in series connections. Such use could result in air embolism due to residual air being drawn from the primary container before administration of the fluid from the secondary container is complete.

Preparation for administration:

1. Suspend container from eyelet support.
2. Remove plastic protector from outlet port at bottom of container.
3. Attach administration set. Refer to complete directions accompanying set.

To prepare PEPCID intravenous solutions, aseptically dilute 2 mL of PEPCID Injection (solution containing 10 mg/mL) with 0.9% Sodium Chloride Injection or other compatible intravenous solution (see *Stability, PEPCID Injection*) to a total volume of either 5 mL or 10 mL and inject over a period of not less than 2 minutes.

To prepare PEPCID intravenous infusion solutions, aseptically dilute 2 mL of PEPCID Injection with 100 mL of 5% dextrose or other compatible solution (see *Stability, PEPCID Injection*), and infuse over a 15-30 minute period.

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Stability

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

PEPCID Injection Premixed

PEPCID Injection Premixed, as supplied premixed in 0.9% sodium chloride in Galaxy® containers (PL 2501 Plastic), is stable through the labeled expiration date when stored under the recommended conditions. (See HOW SUPPLIED, *Storage*.)

PEPCID Injection

When added to or diluted with most commonly used intravenous solutions, e.g., Water for Injection, 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, or Lactated Ringer's Injection, diluted PEPCID Injection is physically and chemically stable (i.e., maintains at least 90% of initial potency) for 7 days at room temperature — see HOW SUPPLIED, *Storage*.

When added to or diluted with Sodium Bicarbonate Injection, 5%, PEPCID Injection at a concentration of 0.2 mg/mL (the recommended concentration of PEPCID intravenous infusion solutions) is physically and chemically

§ Galaxy® is a registered trademark of Baxter International Inc.

stable (i.e., maintains at least 90% of initial potency) for 7 days at room temperature — see HOW SUPPLIED, *Storage*. However, a precipitate may form at higher concentrations of PEPCID Injection (>0.2 mg/mL) in Sodium Bicarbonate Injection, 5%.

HOW SUPPLIED

FOR INTRAVENOUS USE ONLY

No. 3537 — PEPCID Injection Premixed 20 mg per 50 mL is a clear, non-preserved, sterile solution premixed in a vehicle made iso-osmotic with Sodium Chloride, and is supplied as follows:

NDC 0006-3537-50, 50 mL single dose Galaxy® containers (PL 2501 Plastic).

No. 3539 — PEPCID Injection 10 mg per 1 mL, is a non-preserved, clear, colorless solution and is supplied as follows:

NDC 0006-3539-04, 10 x 2 mL single dose vials

No. 3541 — PEPCID Injection 10 mg per 1 mL, is a clear, colorless solution and is supplied as follows:

NDC 0006-3541-14, 4 mL vials

NDC 0006-3541-20, 20 mL vials

NDC 0006-3541-49, 10 x 20 mL vials.

Storage

Store PEPCID Injection Premixed in Galaxy® containers (PL 2501 Plastic) at room temperature (25°C, 77°F). Exposure of the premixed product to excessive heat should be avoided. Brief exposure to temperatures up to 35°C (95°F) does not adversely affect the product.

Store PEPCID Injection at 2-8°C (36-46°F). If solution freezes, bring to room temperature; allow sufficient time to solubilize all the components.

Although diluted PEPCID Injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, it is recommended that if not used immediately after preparation, diluted solutions of PEPCID Injection should be refrigerated and used within 48 hours (see DOSAGE AND ADMINISTRATION).

PEPCID (famotidine) Injection Premixed is manufactured for:
MERCK & CO., INC., West Point, PA 19486, USA

By:
BAXTER HEALTHCARE CORPORATION
Deerfield, Illinois 60015 USA

PEPCID (famotidine) Injection is manufactured by:
MERCK & CO., INC., West Point, PA 19486, USA

Issued ~~March~~XXXXX 2001
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

19-510/S028

20-249/S011

MEDICAL REVIEW(S)

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

Date: April 16, 2002

APPLICATIONS:
NDA 19-510/S-028 Pepcid Injection (famotidine)
NDA 20-249/S-011 Pepcid Injection Premixed (famotidine)

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 19-510/S-028 Pepcid Injection (famotidine)
NDA 20-249/S-011 Pepcid Injection Premixed (famotidine)

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
4/29/02 04:27:44 PM
MEDICAL OFFICER

Hugo Gallo Torres
5/1/02 06:40:36 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

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

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:

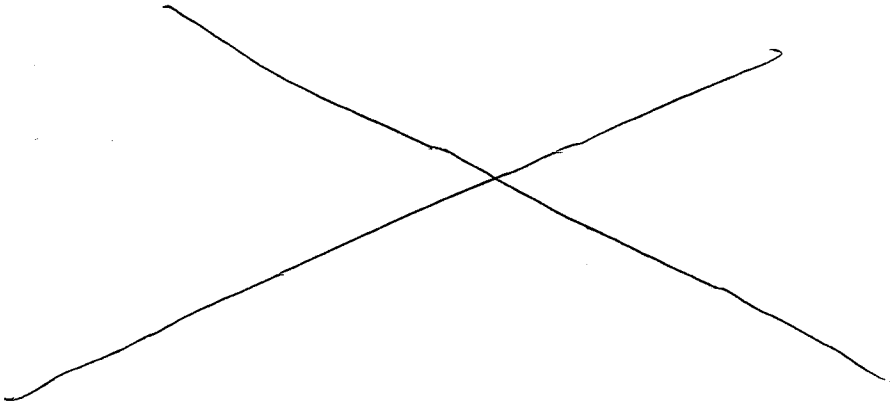
1. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS,** as recommended by FDA Clinical Pharmacology and Biopharmaceutics, delete the sentence: "

"

2. Under **CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS,** delete the new

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)



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

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

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

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

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

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

B. Summary of Clinical Findings:

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

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

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

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

CLINICAL REVIEW

Background and Rationale:

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

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

Materials Submitted and Reviewed:

The application is submitted entirely in electronic format.

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

- Protocol 131 (a placebo-controlled safety and clinical outcomes study in infants up to 1 year);
- Protocol 129 (a PK study in infants up to 1 year);
-

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

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

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

Clinical Studies:

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

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

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

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

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

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

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

The investigational oral formulation was prepared by first preparing [redacted] (See Appendix for description of preparation of formulations). Chemistry portion of the application indicates that sponsor discovered approximately 3.5 months into the study formation of a previously unrecognized degradate [redacted]) when famotidine [redacted] See FDA Chemistry, Manufacturing and Controls Review for further discussion).

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

Schedule of Clinical Observations and Laboratory Measurements

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

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

Data Source: [3.2.1; 3.2.5]

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

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

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

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

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

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

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

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

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

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

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

1. Weight
2. Length
3. Head circumference

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

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

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

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

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

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

K. **Results:**

1. Enrollment and Demographics: Three study sites enrolled a total of 35 patients [redacted], 4 patients; [redacted] 6 patients; [redacted], 25 patients).

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

Baseline Paticnt 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 pateints but no results were available. Few patients had history of apneic episodes. GERD symptoms were mild in most cases. Most infants had been on some therapy within the 30 days prior to entering the study (61% of famotidine 0.5mg patients; 82% of famotidine 1.0mg patients). More famotidine 0.5mg patients had been on cisapride prior to study than had famotidine 1.0mg patients.

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

Disposition of Patients

	Number of Patients		
Observer-Blind Phase:			
			Total
Study Drug	Famotidine 0.5mg	Famotidine 1.0mg	
Patients treated[a]	18	17	35
Completed the study[b]	18	16	34
Completed the phase	14	13	27
Discontinued during the phase: Clinical adverse event Withdrew consent	4 2 2	4 4 0	8 6 2
Continued to double-blind phase	14	13	27

Double-Blind Phase:					
					Total
Double-Blind Phase	Placebo	Famotidine 0.5mg	Placebo	Famotidine 1.0mg	
Patients treated	5	8[c]	6	7	26
Completed the phase	1	2	3	2	8
Switched to marketed formulation	2	2	1	3	8
Discontinued during the phase: Clinical adverse experience Lost to follow-up Therapy ineffective	2 0 1 1	4 1 0 3	2 0 0 2	2 0 0 2	10 1 1 8

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

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

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

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

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

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

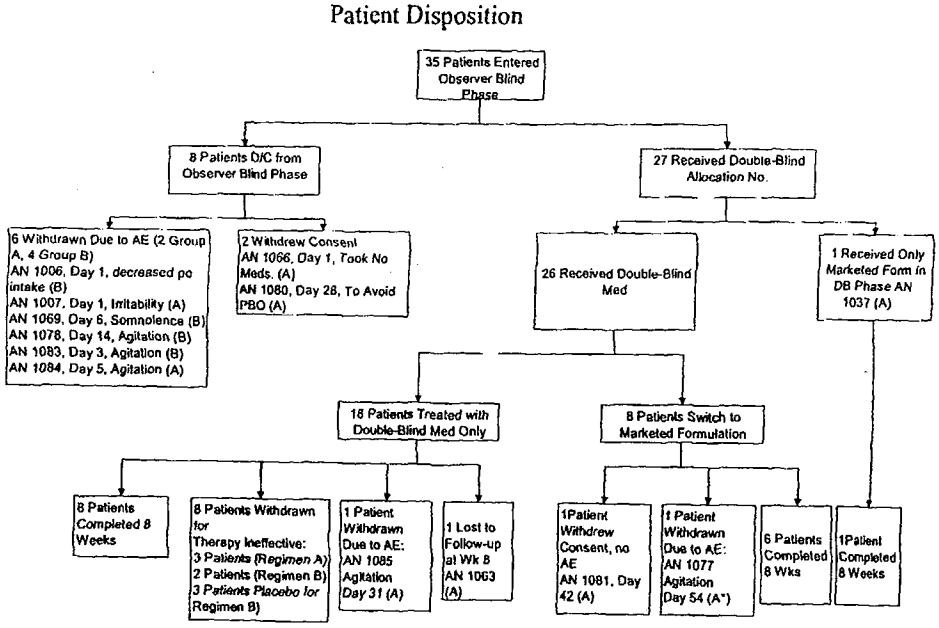


Figure 5—This figure summarizes patient discontinuation. Patients withdrawn due to adverse experiences of agitation, somnolence, or ineffective therapy (lack of efficacy) are identified by allocation number. The regimen being taken at the time of discontinuation is also noted: A=famotidine-0.5 mg/kg/dose;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

Sponsor's diagram

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

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

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

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

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

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

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

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

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

Table 23

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

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

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

Data Source: [4.6]

Table 32

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

		Fam 0.5 mg/Fam 0.5 mg (N=8)†			Fam 0.5 mg/Placebo (N=5)†			Fam 1.0 mg/Fam 1.0 mg (N=6)†			Fam 1.0 mg/Placebo (N=6)†		
	Week	N_1	Measure Mean (std)	Change Mean (std)	N_1	Measure Mean (std)	Change Mean (std)	N_1	Measure Mean (std)	Change Mean (std)	N_1	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_1 = Number of patients with non-missing evaluation.
† All patients are displayed as initially randomized, including those who underwent dose escalation.

Data Source: [4.6]

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

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

Data Source: [4.8]

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

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

Table 62

Details of Neutropenia—Laboratory Adverse Experience

Alloc. No.	Treatment Group	Relative Day	% Neutrophil	Segmented Neutrophil Count

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

Data Source: [4.9]

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

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

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

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

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

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

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

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

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

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

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

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

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

Table 20

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

	Group III Infants (0 to 12 Mo) (n=5)	Children Aged 11 to 15 Yr[†] (n=8)	Geometric Means Ratio (Infants/Children) 95% CI	p-Value	MSE (log-scale)
$AUC_{0-\infty}$ (ng•hr/mL)	609 (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 Dose[†]

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

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

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

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

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

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

† $AUC_{0-24\ hr}$ 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-last} [H+] (mM*hr)	AUC_{0-last} pH (pH*hr)	$AUC_{0-24\ hr}$ [H+] (mM*hr)	$AUC_{0-24\ hr}$ pH pH*hr)	Percentage of Time pH >4[†]	Percentage of Time pH >3[‡]	Number of Hours pH >4	Number of Hours pH >3

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

Data Source: [4.1.9]

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

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

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

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

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.

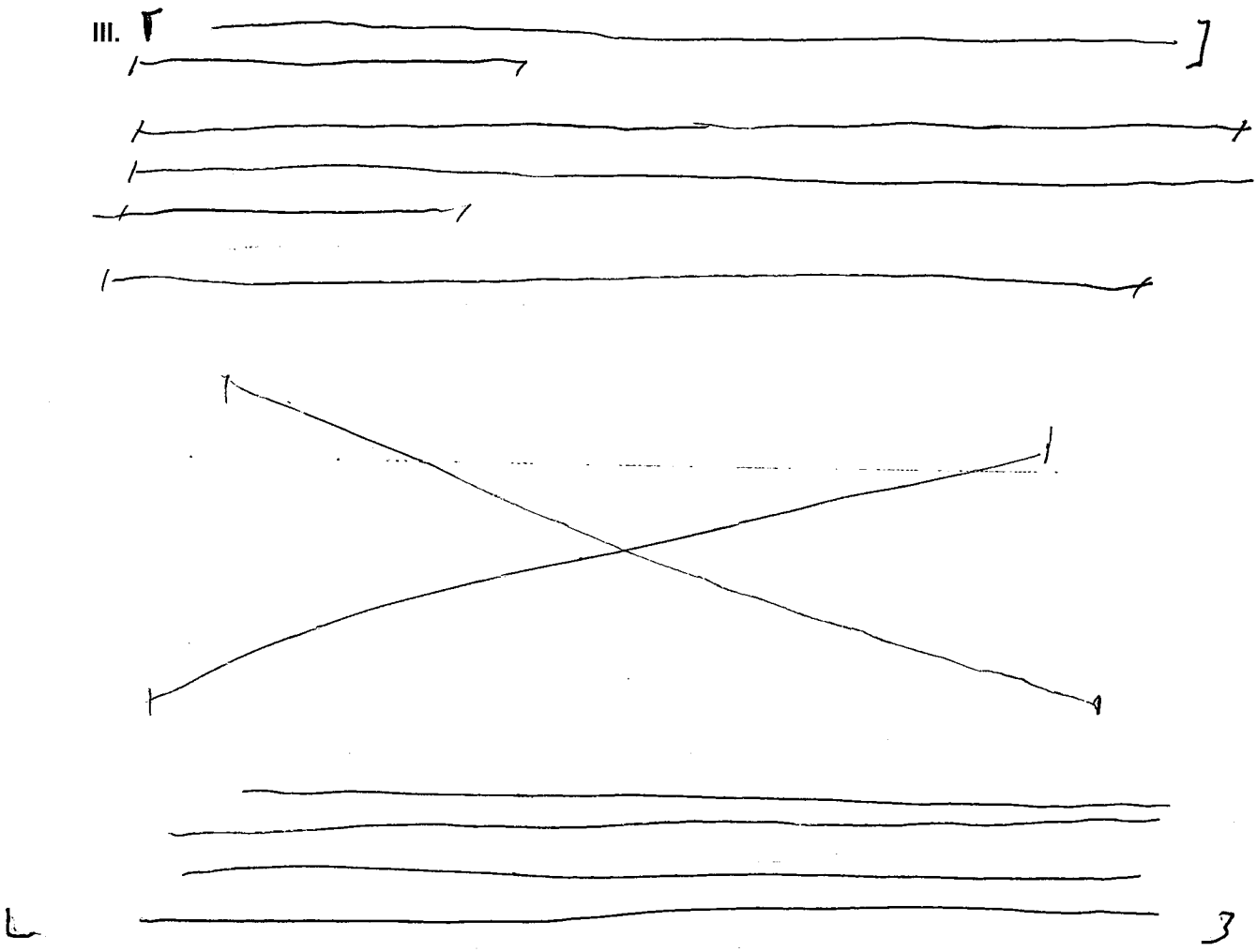
7. Of the 5 infants evaluated for pharmacodynamics, 2 infants 0 to 3 months of age with a gastric pH of 4 or less at baseline had gastric pH increase to >4 for 11 to 26 hours after famotidine doses of 0.25 and 0.5 mg/kg IV, respectively. This prolonged acid suppression is consistent with decreased clearance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

8. Famotidine up to [redacted] 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 [redacted] or 0.5 mg/kg P.O. adjusted by age for once-daily (infants <3 months of age) or twice-daily (infants >3 months of age) dosing is a reasonable initial dose.

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

III. [redacted]



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

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

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

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

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

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

Data Source: [1.1.10; 1.1.12; 4.1.1]

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

Patient	AUC		Percentage of Time pH :		Number of Hours pH :	
	H+ Concentration (mM*hr)	pH (pH*hr)	>4	>3	>4	>3
All Patients (n=11)						
Mean	76.4	132.9	80.6	88.9	19.5	21.6
(95% CI)			(71.3, 89.8)	(83.6, 94.2)	(17.3, 21.8)	(20.3, 22.8)
SD	111.0	23.6	13.8	7.8	3.3	1.9
Median	20.4	134.8	84.2	88.4	20.4	21.4
Geometric mean	19.1	131.0				
(95% CI)	(4.8, 75.6)	(116.2, 147.8)				
SD (log-scale)*	2.048	0.179				
Patients With Baseline pH < 4‡ (n=9)						
Mean			83.5	90.7	20.2	22.0
(95% CI)			(73.6, 93.3)	(85.6, 95.7)	(17.9, 22.6)	(20.8, 23.2)
SD			12.8	6.6	3.1	1.6
Median			85.1	91.8	20.6	22.3

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

Data Source: [4.1.1]

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

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

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

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

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

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

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

reviewer's original table

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

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

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

NOS=not otherwise specified

Reviewer's original table

The two deaths were: (1) a preterm infant (23-24 wks) who was placed on I.V. famotidine deteriorated clinically and died at 12 days; concomitant medications included surfactant, steroids, antibiotics, fentanyl, and dopamine; physician judged death was not related to famotidine, and (2) a 9 month old infant with history of neurological disorder and growth retardation who was hospitalized for unclear reason and receiving multiple medications, including corticosteroids, phenobarbital, [redacted] (ticlofos monosodium salt) and [redacted] (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".

5 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Medical- 19510/5028
20-249/5011

Reviewer's comment: The sponsor should include in the **DOSAGE AND ADMINISTRATION** *section of the labeling for the parenteral formulations information regarding the use of the parenteral products in pediatric patients <1 year of age.*

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 [redacted] A total of 71 patients, 12 of whom were less than 1 month of age, were enrolled in these studies.

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

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

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

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

APPENDIX

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

4. Safety (Cont.)

Table 38

Listing of Patients With Clinical Adverse Experiences—Part I

AN	Age (Days)	Total Daily Dose (mg)	Adverse Experience	Study Day	Duration	Intensity	Serious	Drug Related	Discontinued	Outcome
Part I Patients: Famotidine IV 0 to 3 Months										

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.)										

Data Source: [4.9]

Original protocol (dated October 26, 1999)

Product: MK-0208
Protocol/Amendment No.: 131-00 54

APPENDIX 5

Preparation and Administration of Famotidine for Infants

[redacted]

Protocol Amendment (dated April 19, 2000)

Product: MK-0208
Protocol/Amendment No.: 131-04 16

Change APPENDIX 5 to: (page 54)

APPENDIX 5

Preparation and Administration of Famotidine Oral Suspension for Infants

[redacted]

The suspension may be stored at room temperature [redacted]

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:

19-510/S028

20-249/S011

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

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 bioavalibility 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

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

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)