CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019462, S027

Trade Name: PEPCID TABLETS

Generic Name: FAMOTIDINE

Sponsor: MERCK RESEARCH LABORATORIES

Approval Date: 03/18/99

INDICATION(s): SHORT TERM TREATMENT OF ACTIVE DUODENAL ULCER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 019462, S027

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Printed Labeling				X
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)				X
Bioequivalence Review(s)				X
Administrative/ Correspondence Document(s)	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 019462, S027

APPROVAL LETTER

NDA 19-462/S-027
NDA 19-527/S-020
NDA 20-752/S-002

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

MAR 18 1999

Dear Dr. Kloss:

Please refer to your supplemental new drug applications dated January 27, 1999, received January 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid® (famotidine) Tablets and Pepcid® (famotidine) for Oral Suspension, and Pepcid RPD™ (famotidine) Orally Disintegrating Tablets.

We acknowledge receipt of your correspondence dated February 5, 1999.

These supplements provide for the addition of the following contraindication statement to the end of the **CONTRAINDICATIONS** section of the package insert: "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."

We have completed the review of these supplemental applications 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 January 27, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

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

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

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, contact Michael Folkendt, Regulatory Project Manager, at (301) 827-1602

Sincerely,

/S/ 3-17-99

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019462, S027

MEDICAL REVIEW(S)

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

NDA:	19-462 (SLR027); 19-510 (SLR026); 19-527 (SLR020); 20-249 (SLR009); 20-752 (SLR002)
Sponsor:	Merck Research Laboratories
Drug name:	PEPCID™ (famotidine) Tablets, Injection, Oral Suspension, Injection Premixed, and Orally Disintegrating Tablets
Date submitted:	January 27, 1999
Date Received:	January 28, 1998
Review completed:	March 2, 1999
Reviewer:	Kathy M. Robie-Suh, M.D., Ph.D.

MAR - 3 1999

Among the H_2-receptor antagonists, cross-reactivity with regard to hypersensitivity has been seen in some patients. (See FDA Division of OTC Drug Products review, "Cross-Hypersensitivity Warnings for the OTC H2-Blocker Drug Class" (dated 2/24/99)). Over-the-counter H_2-receptor antagonist products (acid reducers) are being requested to include in the product labeling an allergy warning indicating that cross-sensitivity may exist among the H_2-receptor antagonists. The sponsor has revised the labeling for its OTC famotidine products accordingly.

In this submission the sponsor proposes to revise the CONTRAINDICATIONS section of the package circular for the famotidine prescription drug products to provide labeling consistency between famotidine OTC and prescription products. The sponsor proposes adding the following to the CONTRAINDICATIONS section:

DRAFT LABELING

The application also includes a few minor editorial and formatting changes.

These changes are being made as a Changes-Being-Effected supplemental application to the above cited NDAs.

Also, the sponsor requests that the Agency provide to Merck & Co. copies of the reports of cross-sensitivity.

Reviewer's Comments and Recommendations:
The sponsor's proposed labeling revision is acceptable. I recommend that this application be approved.

The sponsor should be provided with the 6 cases of cross-hypersensitivity reactions identified in the 2/25/99 OTC review cited above.

/S/

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

3/3/99

Concur. March 3, 1999

/S/

cc:
NDA 19-462;
19-510;
19-527;
20-249;
20-752
HFD-180
HFD-180/LTalarico
HFD-180/HGallo-Torres
HFD-180/KRobie-Suh
HFD-181/MFolkendt
HFD-180/JChoudary
HFD-180/EDuffy
f/t 3/3/99 jgw
N/19462903.0KR

/S/ 3-3-99

7825031

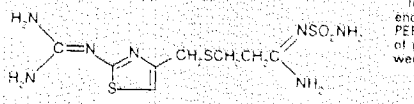
MERCK & CO., INC.
West Point, PA 19486, USA

APPROVED

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

DESCRIPTION

The active ingredient in PEPCID® (famotidine) 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.

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

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

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

CLINICAL PHARMACOLOGY IN ADULTS

GI Effects

PEPCID is a competitive inhibitor of histamine 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.

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

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

Other Effects

Systemic effects of PEPCID on 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.

PEPCID® (famotidine) Tablets
PEPCID® (famotidine) for Oral Suspension
PEPCID RPD™ (famotidine) Orally Disintegrating Tablets

Pharmacokinetics

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

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

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of PEPCID.

Clinical Studies

Duodenal Ulcer

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

Table 1
Outpatients with Endoscopically Confirmed Healed Duodenal Ulcers

	PEPCID 40 mg h.s. (N = 85)	PEPCID 20 mg b.i.d. (N = 84)	Placebo h.s. (N = 97)
Week 2	**32%	**28%	17%
Week 4	**70%	**67%	31%

**Statistically significantly different than placebo ($p \leq 0.001$)

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 ($p \leq 0.01$). 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 ($p \leq 0.01$).

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 (opposite 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	*68%	44%	*65%	46%
Week 8	**78%	64%	*80%	54%

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

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

PEPCID® (famotidine) Tablets
PEPCID® (famotidine) for Oral Suspension
PEPCID RPD™ (famotidine) Orally Disintegrating Tablets

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. h.s. 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=126)	Placebo (N=68)
Week 6	49*††	32*	16
Week 12	80*††	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 q.d. h.s. was compared to ranitidine 150 mg 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 q.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†††	66	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

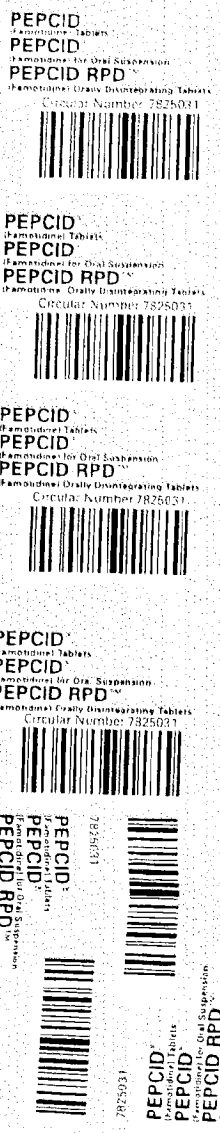
Table 6 presents pharmacokinetic data from published studies of small numbers of pediatric patients given famotidine intravenously. Areas under the curve (AUCs) are normalized to a dose of 0.5 mg/kg I.V. for pediatric patients and compared with an extrapolated 40 mg intravenous dose in adults (extrapolation based on results obtained with a 20 mg I.V. adult dose).

Table 6
Pharmacokinetic Parameters in Intravenously Famotidine

Age (Number of Patients)	Area Under the Curve (AUC) (ng•hr/mL)	Total Clearance (CL) (L/hr/kg)	Volume of Distribution (Vd) (L/kg)	Elimination Half-life (T½) (hours)
1-11 yrs (N=20)	1089 ± 304	0.54 ± 0.14	2.03 ± 7.4%	3.39 ± 7.6%
11-15 yrs (N=6)	1143 ± 320	0.48 ± 0.14	1.5 ± 0.4	2.2 ± 0.4
Adults (N=7)	1725	0.29 ± 0.13	1.3 ± 0.2	2.83 ± 0.59

Values are expressed as the mean ± SD unless indicated otherwise.
N=number of pts.

Values of pharmacokinetic parameters for pediatric patients, ages 1-15 years, are comparable to those obtained for adults.



7825031

PEPCID® (famotidine) Tablets
PEPCID® (famotidine) for Oral Suspension
PEPCID RPD™ (famotidine) Orally Disintegrating Tablets

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 an AUC of 560 ± 60 ng·hr/mL in pediatric patients 11-15 years of age 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)[a]
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 ± 10.5

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

Four 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	Number of Patients
0.3 mg/kg, single dose	I.V.	gastric pH >3.5 for 8.7 ± 4.7[b] hours	6
0.4-0.8 mg/kg	I.V.	gastric pH >4 for 5-9 hours	15
0.5 mg/kg, single dose	I.V.	≥ 2 pH unit increase above baseline in gastric pH for >8 hours	9
0.5 mg/kg b.i.d.	I.V.	gastric pH >5 for 12.5 ± 1.3[b] hours	4
0.5 mg/kg b.i.d.	oral	gastric pH >5 for 5.3 ± 1.3[b] hours	4

[a]Values reported in published literature.
[b]Means ± SD.

INDICATIONS AND USAGE

PEPCID is indicated in:

1. *Short term treatment of active duodenal ulcer.* Most adult patients heal within 4 weeks; there is rarely reason to use PEPCID at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than eight weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies in adults have not extended beyond one year.

3. *Short term treatment of active benign gastric ulcer.* Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

4. *Short term treatment of gastroesophageal reflux disease (GERD).* PEPCID is indicated for short term treatment of patients with symptoms of GERD (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

PEPCID is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)* (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

CONTRAINDICATIONS

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, PEPCID should not be administered to patients with a history of hypersensitivity to other H_2-receptor antagonists.

PRECAUTIONS

General

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

Patients with Severe Renal Insufficiency

Longer intervals between doses or lower doses may need to be used in patients with severe renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. (See CLINICAL PHARMACOLOGY IN ADULTS and DOSAGE AND ADMINISTRATION.) However, currently, no drug-related toxicity has been found with high plasma concentrations of famotidine.

Information for Patients

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

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

PEPCID® (famotidine) Tablets
PEPCID® (famotidine) for Oral Suspension
PEPCID RPD™ (famotidine) Orally Disintegrating Tablets

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

Drug Interactions

No drug interactions have been identified. Studies with famotidine in man in animal models and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine; indocyanine green as an index of hepatic blood 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 overt teratogenic 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 500 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

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

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

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

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

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

Use in Elderly Patients

No dosage adjustment is required based on age (see CLINICAL PHARMACOLOGY IN ADULTS, *Pharmacokinetics*). Dosage adjustment in the case of severe renal impairment may be necessary.

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 Tab-

ters, 40 mg at bedtime, was similar to that in the placebo group.

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

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

Body as a Whole: fever, asthenia, fatigue

Cardiovascular: arrhythmia, AV block, palpitation

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

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

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

Musculoskeletal: musculoskeletal pain including muscle cramps, arthralgia

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

Respiratory: bronchospasm

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

Special Senses: tinnitus, taste disorder

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

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

OVERDOSAGE

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

The oral 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. The intravenous LD_{50} of famotidine for mice and rats ranged from 254-553 mg/kg and the minimum lethal single I.V. dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in I.V. treated dogs were emesis, restlessness, pallor of mucous membranes or redness of mouth and ears, hypotension, tachycardia and collapse.

DOSAGE AND ADMINISTRATION

Duodenal Ulcer

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

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

Benign Gastric Ulcer

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

Gastroesophageal Reflux Disease (GERD)

The recommended oral dosage for treatment of adult patients with symptoms of GERD is 20 mg b.i.d. for up to 6 weeks. The recommended oral dosage for the treatment of adult patients with esophagitis including erosions and ulcerations and accompanying symptoms due to GERD is 20 or 40 mg b.i.d. for up to 12 weeks (see CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies*).

Dosage for Pediatric Patients

See PRECAUTIONS, *Pediatric Patients*.

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

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

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

While published uncontrolled studies suggest effectiveness of famotidine in the treatment of gastroesophageal reflux disease and peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (usually based on adult duration recommendations) and dose should be individualized based on clinical response and/or pH determination (gastric or esophageal) and endoscopy. Published uncontrolled clinical studies in pediatric patients have employed doses up

to 1 mg/kg/day for peptic ulcer and 2 mg/kg/day for GERD with or without esophagitis including erosions and ulcerations.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

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

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

Oral Suspension

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

Directions for Preparing PEPCID for Oral Suspension

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

Stability of PEPCID for Oral Suspension

Unused constituted oral suspension should be discarded after 30 days.

Orally Disintegrating Tablets

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

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

Concomitant Use of Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In adult patients with severe renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min, the elimination half-life of PEPCID may exceed 20 hours, reaching approximately 24 hours in anuric patients. Although no relationship of adverse effects to high plasma levels has been established, to avoid excess accumulation of the drug, the dose of PEPCID may be reduced to 20 mg h.s. 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 severe renal insufficiency should be considered.

HOW SUPPLIED

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

NDC 0006-0963-31 unit of use bottles of 30
NDC 0006-0963-94 unit of use bottles of 90
NDC 0006-0963-58 unit of use bottles of 100
NDC 0006-0963-28 unit dose package of 100
NDC 0006-0963-82 bottles of 1,000
NDC 0006-0963-87 bottles of 10,000
NDC 0006-0963-72 carton of 25 UNIBLISTER™ cards of 31 tablets each.

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

NDC 0006-0964-31 unit of use bottles of 30
NDC 0006-0964-94 unit of use bottles of 90
NDC 0006-0964-58 unit of use bottles of 100
NDC 0006-0964-28 unit dose package of 100
NDC 0006-0964-82 bottles of 1,000
NDC 0006-0964-87 bottles of 10,000
NDC 0006-0964-72 carton of 25 UNIBLISTER™ cards of 31 tablets each.

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

NDC 0006-3553-31 unit dose package of 30
NDC 0006-3553-48 unit dose package of 100
NDC 0006-3553-28 unit dose package of 100

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

NDC 0006-3554-31 unit dose package of 30
NDC 0006-3554-48 unit dose package of 100

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

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

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

NDA 20-752

PEPCID® (famotidine) Tablets
PEPCID® (famotidine) for Oral Suspension
PEPCID RPD™ (famotidine) Orally Disintegrating Tablets

Storage

Avoid storage of PEPCID Tablets at temperatures above 40°C (104°F).

Store PEPCID RPD Orally Disintegrating Tablets below 30°C (86°F).

Avoid storage of the powder for oral suspension at temperatures above 40°C (104°F). After constitution store the suspension below 30°C (86°F). Do not freeze. Discard unused suspension after 30 days.

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

MERCK & CO., INC., West Point, PA 19486 USA

PEPCID RPD (famotidine) Orally Disintegrating Tablets are manufactured for

MERCK & CO., INC., West Point, PA 19486 USA

By
Schering-Plough Ltd., Swindon, England and are
Made in England

Issued November 1998
Printed in USA

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019462, S027

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

Division of Gastrointestinal and Coagulation Drug Products

CONSUMER SAFETY OFFICER LABELING REVIEW

NDA number	Supplement number	Drug Name
19-462	SLR-027	Pepcid® (famotidine) Tablets
19-527	SLR-020	Pepcid® (famotidine) for Oral Suspension
20-752	SLR-002	Pepcid RPD™ (famotidine) Orally Disintegrating Tablets

Sponsor: Merck Research Laboratories

MAR 17 1999

Material Reviewed

Submission Date	Receipt Date	Item(s) Reviewed
January 27, 1999	January 28, 1999	Final Printed Labeling (FPL), ID # **7825031**
February 5, 1999	February 8, 1999	Diskette (formatted labeling text in MS Word 97) Filename: **7825031.doc**

Background

These supplements, submitted as Special Supplement – Changes Being Effected," provides for the addition of the following contraindication statement to the end of the **CONTRAINDICATIONS** section of the package insert:

> "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."

The firm submitted these supplements to make the contraindication statement in the prescription package insert consistent with the recently required allergy warning statement for the nonprescription Pepcid AC® (famotidine) drug products labeling. This allergy warning statement, "Do not use if you are allergic to Pepcid AC® (famotidine) or other acid reducers," required by the Division of Over-The-Counter Drug Products, originated from the discovery of a number of Adverse Event reports suggesting cross-sensitivity within the class of H_2-receptor antagonist (see medical officers review dated 2/24/99 to NDA 20-325). The stated effective date for this change is "on or about July 1, 1999."

Review

All oral dosage forms of Pepcid® (famotidine) for prescription use share the same package insert. The submitted final printed labeling (FPL) for the package insert, identified as circular #**7825031** (filename 7825031.doc), **Issued November 1998**, was compared to the approved labeling identified as circular #7825030, Issued August 1998 (acknowledged and retained on January 21, 1999 in NDAs 19-462/SLR-022, 19-527/SLR-016, and 20-752/SLR-001).

The following changes were made to the package insert:

1. The statement DRAFT LABELING [redacted] was added to the end of the **CONTRAINDICATIONS** section. **This change is the subject of these supplements and was found acceptable in the March 3, 1999 Medical Officer's Review.**

2. The first letter of the established name "famotidine" is changed from upper case to lower case throughout the labeling, except in the drug name title at the beginning of the labeling. **This editorial change makes the established name more consistent with the convention used by the Agency and is acceptable.**

3. The word [redacted] is deleted from the forth paragraph of the DESCRIPTION section concerning the description of the orally disintegrating tablet dosage form. **This change was made to make this paragraph editorially consistent with similar paragraphs concerning the description of the tablet and oral suspension dosage forms and is acceptable.**

4. The national stock numbers (NSN) were removed from the HOW SUPPLIED section. These numbers were the "(6505 01 XXX XXXX)" under a number of NDC numbers and correspond to product codes (corresponding to the respective NDC number above it) used by the Veteran's Administration for the corresponding package configuration. **Because, there are no regulatory requirements for the inclusion of these national stock numbers in the package insert, the deletion of these numbers is acceptable.**

5. A space was added between "No." and the numbers "3553" and "3554" to correct a minor editorial formatting error.

Conclusions

The FPL identified as circular # **7825031, Issued November 1998**, is acceptable. An approval letter should be issued to these supplements.

/S/ [redacted] 3/17/99
Regulatory Project Manager

Concur /S/ [redacted] 3-17-99

NDA 19-462/S-027
NDA 19-510/S-026
NDA 19-527/S-020
NDA 20-249/S-009
NDA 20-752/S-002

MAR - 4 1999

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

Dear Dr. Kloss:

We acknowledge receipt of your labeling supplemental applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA Number	Supplement Number	Drug Name
19-462	S-027	Pepcid® (famotidine) Tablets
19-510	S-026	Pepcid® (famotidine) Injection
19-527	S-020	Pepcid® (famotidine) for Oral Suspension
20-249	S-009	Pepcid® (famotidine) Injection Premixed
20-752	S-002	Pepcid RPD™ (famotidine) Orally Disintigrating Tablets

Date of Supplements: January 27, 1999

Date of Receipt: Janauary 28, 1999

These supplements propose to add the following contraindication statement to the end of the CONTRAINDICATIONS section of the package insert: "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."

We note that you have submitted these supplements under 21 CFR 314.70(c), "Special Supplement - Changes Being Effected." Your submissions states that the implementation date for this change is on or before July 1, 1999.

Unless we notify you within 60 days of our receipt date that the applications are not sufficiently complete to permit a substantive review, these applications will be filed under section 505(b) of the Act on March 29, 1999 in accordance with 21 CFR 314.101(a).

Please cite the application numbers 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, contact me at (301) 827-1602.

Sincerely,

/S/ [redacted] 3/4/99

Michael Folkendt
Regulatory Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDAs 19-462, 19-510, 19-527, 20-249, 20-752
HFD-180/Div. Files
HFD-180/M.Folkendt
DISTRICT OFFICE

Drafted by: mmf/March 4, 1999
final: 3/4/99
filename: 19462-S027-ACK.doc

SUPPLEMENT ACKNOWLEDGEMENT (AC)

NDA 19-510/S-026
NDA 20-249/S-009

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

MAR 5 1999

Dear Dr. Kloss:

Please refer to your supplemental new drug applications dated January 27, 1999, received January 28, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pepcid® (famotidine) Injection and Injection Premixed.

We acknowledge receipt of your correspondence dated February 5, 1999.

These supplements provide for the addition of the following contraindication statement to the end of the **CONTRAINDICATIONS** section of the package insert: "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."

We have completed the review of these supplemental applications 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 January 27, 1999). Accordingly, these supplemental applications are approved effective on the date of this letter.

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

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

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, contact Michael Folkendt, Regulatory Project Manager, at (301) 827-1602

Sincerely,

/S/ 3-4-99

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

Division of Gastrointestinal and Coagulation Drug Products

CONSUMER SAFETY OFFICER LABELING REVIEW

NDA number	Supplement number	Drug Name
19-510	SLR-026	Pepcid® (famotidine) Injection
20-249	SLR-009	Pepcid® (famotidine) Injection Premixed

Sponsor: Merck Research Laboratories

MAR 17 1999

Material Reviewed

Submission Date	Receipt Date	Item(s) Reviewed
January 27, 1999	January 28, 1999	Final Printed Labeling (FPL), ID # **9042508**
February 5, 1999	February 8, 1999	Diskette (formatted labeling text in MS Word 97) Filename: **9042508.doc**

Background

These supplements, submitted as Special Supplement – Changes Being Effected," provides for the addition of the following contraindication statement to the end of the **CONTRAINDICATIONS** section of the package insert:

DRAFT LABELING

[redacted]

The firm submitted these supplements to make the contraindication statement in the prescription package insert consistent with the recently required allergy warning statement for the nonprescription Pepcid AC® (famotidine) drug products labeling. This allergy warning statement, "Do not use if you are allergic to Pepcid AC® (famotidine) or other acid reducers," required by the Division of Over-The-Counter Drug Products, originated from the discovery of a number of Adverse Event reports suggesting cross-sensitivity within the class of H_2-receptor antagonist (see medical officers review dated 2/24/99 to NDA 20-325). The stated effective date for this change is "on or about July 1, 1999."

Review

All parenteral dosage forms of Pepcid® (famotidine) for prescription use share the same package insert. The submitted final printed labeling (FPL) for the package insert, identified as circular # **9042508** (filename 9042508.doc), **Issued November 1998**, was compared to the approved

labeling identified as circular # 9042507, Issued August 1998 (acknowledged and retained on January 20, 1999 in NDAs 19-510/SLR-020 and 20-249/SLR-007).

The following changes were made to the package insert:

1. The statement [redacted] was added to the end of the **CONTRAINDICATIONS** section. **This change is the subject of these supplements and was found acceptable in the March 3, 1999, Medical Officer's Review.**

2. The secondary control number located either immediately below or after the circular ID # has been changed from "07-19-04-689" to "07-19-04-822." According to the firm, this control number is for use by Baxter Healthcare Corporation who manufactures the premixed injection formulation. **This change does not change the content of the labeling concerning the safe use of the drug and is acceptable.**

3. [redacted] **This change adds the recently approved oral dosage form to this statement and makes this statement consistent with the similar statement in the package insert for the oral dosage forms. This change is acceptable.**

4. In the DOSAGE AND ADMINISTRATION section:

5. Immediately below the title of the "Dosage for Pediatric Patients" subsection, the phrase [redacted]" has been indented. **This editorial revision is acceptable.**

6. The period at the end of the parenthetical phrase "(See HOW SUPPLIED, Storage.)" in the "PEPCID Injection Premixed" subsection has been moved to inside the closing parentheses [redacted] **This editorial revision corrects a minor punctuation error and is acceptable.**

7. The national stock numbers (NSN) were removed from the HOW SUPPLIED section. These numbers were the "(6505 01 XXX XXXX)" under a number of NDC numbers and correspond to product codes (corresponding to the respective NDC number above it) used by the Veteran's Administration for the corresponding package configuration. **Because, there**

are no regulatory requirements for the inclusion of these national stock numbers in the package insert, the deletion of these numbers is acceptable.

Conclusions

The FPL identified as circular # **9042508, Issued November 1998**, is acceptable. An approval letter should be issued to these supplements.

/S/ 3/17/99
Regulatory Project Manager

/S/ 3-17-99

cc:
Archival NDA 19-510
NDA 20-249
HFD-180/Div. Files for NDAs 19-510 & 20-249
HFD-180/M.Folkendt

draft: mmf/March 15, 1999
final: 3/17/99
filename: 19510-SLR026-LBLreview.DOC

CSO LABELING REVIEW

APPEARS THIS WAY
ON ORIGINAL

NDA 19-462/S-027
NDA 19-527/S-020
NDA 19-510/S-026
NDA 20-249/S-009
NDA 20-752/S-002

MAR 12 1999

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

Dear Dr. Kloss:

Please refer to your supplemental new drug applications for Pepcid® (famotidine) Tablets, for Oral Suspension, Injection, Injection Pre-Mixed, and Pepcid RPD™ (famotidine) Orally Disintegrating Tablets.

Regarding your request for copies of the adverse event reports received by the Agency suggesting cross-sensitivity within the class of H_2-receptor antagonist, your request should be directed to the new drug applications (NDA) for non-prescription Pepcid AC® at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Over-The-Counter Drug Products, HFD-560
9201 Corporate Blvd.
Rockville, MD 20850

If you have any questions, contact Michael Folkendt, Project Manager, at (301) 827-1602.

Sincerely,

/S/ 3-12-99

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