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
**APPLICATION:** 019462, S027

**CONTENTS**

<table>
<thead>
<tr>
<th></th>
<th>Included</th>
<th>Pending Completion</th>
<th>Not Prepared</th>
<th>Not Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approval Letter</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tentative Approval Letter</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Approvable Letter</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Printed Labeling</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Medical Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Chemistry Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>EA/FONSI</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Pharmacology Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Statistical Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Microbiology Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Clinical Pharmacology</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Biopharmaceutics Review(s)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioequivalence Review(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Administrative/</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correspondence Document(s)</td>
<td></td>
<td></td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>
Application Number: 019462, S027

APPROVAL LETTER
Dear Dr. Kloss:


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 H2-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,

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.

Among the H₂-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 H₂-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 H₂-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-Effectuated 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.

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

Kathy M. Robie-Suh, M.D., Ph.D.
March 3, 1999

Concur.
PEPCID® (FAMOTIDINE) TABLETS

DESCRIPTION

The active ingredient in PEPCID® (famotidine) is a highly stable, non-competitive, histamine H2-receptor antagonist, famotidine dihydrochloride. Famotidine dihydrochloride is the dihydrochloride salt of 1-(2-furyl)-2-[[(2-METHYL-1H-IMIDAZOL-4-YL)-METHYL]AMINO]-ETHANONE DIHYDROCHLORIDE. The chemical name is: 1-(2-furyl)-2-[[(2-METHYL-1H-IMIDAZOL-4-YL)-METHYL]AMINO]-ETHANONE DIHYDROCHLORIDE. The molecular formula is \( \text{C}_{14}\text{H}_{16}\text{N}_{2}\text{O}_{3}\text{HCl} \) and the molecular weight is 337.34, as a USP standard.

PHARMACOLOGICAL PROPERTIES

PEPCID® (famotidine) is an H2-receptor antagonist which exerts its action by selectively blocking the binding of histamine to its receptor in the parietal cell. This blocks the binding of histamine to the H2-receptor, inhibiting the synthesis of acid by the parietal cell. The inhibition of acid secretion by PEPCID® is dose-related to the dose of famotidine.

INDICATIONS

PEPCID® (famotidine) is indicated for the treatment of gastrointestinal conditions caused by hypersecretion of acid, including duodenal ulcer disease, benign gastric ulcer disease, GERD (gastroesophageal reflux disease), ulcer-like conditions, and gastric hypersecretory states. It is also indicated for the prevention of gastric and duodenal ulcer recurrence.

CONTRAINDICATIONS

PEPCID® (famotidine) is contraindicated in patients with known hypersensitivity to the drug. It is not recommended for use in patients with acute peptic ulcer disease or in patients with known peptic ulcer hemorrhage requiring hospitalization.

WARNINGS AND PRECAUTIONS

PEPCID® (famotidine) should be used with caution in patients with hepatic or renal impairment. In patients with severe hepatic impairment, the pharmacokinetics of famotidine may be altered, resulting in increased plasma levels.

ADVERSE REACTIONS

The most common adverse reactions associated with PEPCID® are constipation, diarrhea, headache, and abdominal pain.

DRUG INTERACTIONS

Famotidine may increase the plasma levels of other drugs that are metabolized by CYP2C19, such as warfarin and salicylates.

DOSE AND ADMINISTRATION

The usual dose of PEPCID® for adults and children 12 years of age and older is 10 mg once daily, with or without food. The dose for children under 12 years of age is 1 mg/kg once daily, with or without food.

PEPCID® RPD™ (FAMOTIDINE) FOR ORAL SUSPENSION

The suspension of PEPCID® (famotidine) is indicated for the treatment of gastroesophageal reflux disease (GERD) in adults and children 12 years of age and older. The recommended dosage is 10 mg once daily taken 2 hours after meals.

PEPCID® ORALLY DISINTEGRATING TABLETS

The oral disintegrating tablets of PEPCID® (famotidine) should be taken on an empty stomach, at least 1 hour before or 2 hours after meals, with one glass of water.

CLINICAL PHARMACOLOGY IN ADULTS

GI Effects

PEPCID® (famotidine) is a histamine H2-receptor antagonist, which inhibits acid secretion by blocking histamine-induced stimulation of parietal cells. This results in a decrease in acid production, which is associated with the inhibition of proton pumps (H+/K+ ATPase).

Additional Information

A single dose of famotidine produces a rapid increase in gastric pH, resulting in the inhibition of acid secretion. The gastric pH returns to baseline within 2-4 hours after the dose. Famotidine has a long half-life, with a plasma elimination half-life of approximately 4.5-6.5 hours.

Table

<table>
<thead>
<tr>
<th>Week</th>
<th>PEPCID® Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mg once daily</td>
</tr>
<tr>
<td>2</td>
<td>10 mg once daily</td>
</tr>
</tbody>
</table>

This information is intended for educational purposes only and should not be used as a substitute for professional medical advice. Always consult a healthcare provider for medical advice, diagnosis, or treatment.

APPEARS THIS WAY ON ORIGINAL
BEST POSSIBLE COPY

APPEARS THIS WAY ON ORIGINAL

INDICATIONS AND USAGE
PEPCID is indicated for:
1. Short-term treatment of active duodenal ulcer in adult patients. PEPCID is used in the maintenance phase of treatment in patients who have had an active ulcer for 8 to 12 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks for evidence of ulcer healing. If no healing is observed after 8 weeks, PEPCID should not be prescribed for additional treatment of the ulcer. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
2. Maintenance therapy for chronic active duodenal ulcers in adult patients. PEPCID is indicated for the maintenance therapy of chronic active duodenal ulcers in adult patients who have had an active ulcer for 8 to 12 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
3. Short-term treatment of active duodenal ulcer in adult patients. PEPCID is indicated for the short-term treatment of active ulcers in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
4. Short-term treatment of active duodenal ulcer in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
5. Short-term treatment of active duodenal ulcer in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
6. Short-term treatment of active duodenal ulcer in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.

CONTRAINDICATIONS
Hypersensitivity to cimetidine or any component of this product. Cimetidine has been associated with a low incidence of anaphylactoid reactions. Therefore, PEPCID should be used only when the benefit of therapy outweighs the potential adverse effects.

PRECAUTIONS
General
Symptomatic response to therapy with PEPCID does not indicate a maximum response to treatment. Patients with severe peptic ulcer-related symptoms should be observed carefully. Patients with severe peptic ulcer-related symptoms should be observed carefully.

Patients with Severe Renal Impairment
Limited information is available on the use of PEPCID in patients with severe renal impairment. Therefore, PEPCID should be used with caution in these patients.

ADVERSE REACTIONS
The adverse reaction profile of PEPCID is similar to that of other H2 receptor antagonists. The most common adverse effects reported with PEPCID are headache, nausea, and constipation. Other adverse effects reported with PEPCID include gastrointestinal symptoms, such as diarrhea, abdominal pain, and flatulence. These adverse effects are generally mild to moderate in severity and are usually reversible upon discontinuation of the medication.

NDA 20-21

ADVERSE REACTIONS
The most common adverse events reported with PEPCID are headache, nausea, and constipation. Other adverse effects reported with PEPCID include gastrointestinal symptoms, such as diarrhea, abdominal pain, and flatulence. These adverse effects are generally mild to moderate in severity and are usually reversible upon discontinuation of the medication.

PEPCID is indicated for:
1. Short-term treatment of active duodenal ulcer in adult patients. PEPCID is used in the maintenance phase of treatment in patients who have had an active ulcer for 8 to 12 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks for evidence of ulcer healing. If no healing is observed after 8 weeks, PEPCID should not be prescribed for additional treatment of the ulcer. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
2. Maintenance therapy for chronic active duodenal ulcers in adult patients. PEPCID is indicated for the maintenance therapy of chronic active duodenal ulcers in adult patients who have had an active ulcer for 8 to 12 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
3. Short-term treatment of active duodenal ulcer in adult patients. PEPCID is indicated for the short-term treatment of active ulcers in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
4. Short-term treatment of active duodenal ulcer in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
5. Short-term treatment of active duodenal ulcer in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.
6. Short-term treatment of active duodenal ulcer in adult patients who have had an active ulcer for less than 8 weeks. Studies have not assessed the efficacy of PEPCID in patients who have had an active ulcer for less than 8 weeks. Patients should be reassessed at 8 weeks following completion of an appropriate ulcer healing course.

CONTRAINDICATIONS
Hypersensitivity to cimetidine or any component of this product. Cimetidine has been associated with a low incidence of anaphylactoid reactions. Therefore, PEPCID should be used only when the benefit of therapy outweighs the potential adverse effects.

PRECAUTIONS
General
Symptomatic response to therapy with PEPCID does not indicate a maximum response to treatment. Patients with severe peptic ulcer-related symptoms should be observed carefully. Patients with severe peptic ulcer-related symptoms should be observed carefully.

Patients with Severe Renal Impairment
Limited information is available on the use of PEPCID in patients with severe renal impairment. Therefore, PEPCID should be used with caution in these patients.

ADVERSE REACTIONS
The adverse reaction profile of PEPCID is similar to that of other H2 receptor antagonists. The most common adverse effects reported with PEPCID are headache, nausea, and constipation. Other adverse effects reported with PEPCID include gastrointestinal symptoms, such as diarrhea, abdominal pain, and flatulence. These adverse effects are generally mild to moderate in severity and are usually reversible upon discontinuation of the medication.

NDA 20-21

ADVERSE REACTIONS
The most common adverse events reported with PEPCID are headache, nausea, and constipation. Other adverse effects reported with PEPCID include gastrointestinal symptoms, such as diarrhea, abdominal pain, and flatulence. These adverse effects are generally mild to moderate in severity and are usually reversible upon discontinuation of the medication.
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 019462, S027

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS
CONSUMER SAFETY OFFICER LABELING REVIEW

<table>
<thead>
<tr>
<th>NDA number</th>
<th>Supplement number</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-462</td>
<td>SLR-027</td>
<td>Pepcid® (famotidine) Tablets</td>
</tr>
<tr>
<td>19-527</td>
<td>SLR-020</td>
<td>Pepcid® (famotidine) for Oral Suspension</td>
</tr>
<tr>
<td>20-752</td>
<td>SLR-002</td>
<td>Pepcid RPD™ (famotidine) Orally Disintegrating Tablets</td>
</tr>
</tbody>
</table>

Sponsor: Merck Research Laboratories

Material Reviewed

<table>
<thead>
<tr>
<th>Submission Date</th>
<th>Receipt Date</th>
<th>Item(s) Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 27, 1999</td>
<td>January 28, 1999</td>
<td>Final Printed Labeling (FPL), ID # 7825031</td>
</tr>
<tr>
<td>February 5, 1999</td>
<td>February 8, 1999</td>
<td>Diskette (formatted labeling text in MS Word 97)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Filename: 7825031.doc</td>
</tr>
</tbody>
</table>

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 H₂-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 H₂-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 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 [ ] is deleted from the fourth 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.
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:

<table>
<thead>
<tr>
<th>NDA Number</th>
<th>Supplement Number</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-462</td>
<td>S-027</td>
<td>Pepcid® (famotidine) Tablets</td>
</tr>
<tr>
<td>19-510</td>
<td>S-026</td>
<td>Pepcid® (famotidine) Injection</td>
</tr>
<tr>
<td>19-527</td>
<td>S-020</td>
<td>Pepcid® (famotidine) for Oral Suspension</td>
</tr>
<tr>
<td>20-249</td>
<td>S-009</td>
<td>Pepcid® (famotidine) Injection Premixed</td>
</tr>
<tr>
<td>20-752</td>
<td>S-002</td>
<td>Pepcid RPD™ (famotidine) Orally Disintegrating Tablets</td>
</tr>
</tbody>
</table>

Date of Supplements: January 27, 1999

Date of Receipt: January 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 H₂-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,

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)
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 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 H2-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,

[Signature]

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

<table>
<thead>
<tr>
<th>NDA number</th>
<th>Supplement number</th>
<th>Drug Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-510</td>
<td>SLR-026</td>
<td>Pepcid® (famotidine) Injection</td>
</tr>
<tr>
<td>20-249</td>
<td>SLR-009</td>
<td>Pepcid® (famotidine) Injection Premixed</td>
</tr>
</tbody>
</table>

Sponsor: Merck Research Laboratories

Material Reviewed

<table>
<thead>
<tr>
<th>Submission Date</th>
<th>Receipt Date</th>
<th>Item(s) Reviewed</th>
</tr>
</thead>
<tbody>
<tr>
<td>January 27, 1999</td>
<td>January 28, 1999</td>
<td>Final Printed Labeling (FPL), ID # 9042508</td>
</tr>
<tr>
<td>February 5, 1999</td>
<td>February 8, 1999</td>
<td>Diskette (formatted labeling text in MS Word 97) Filename: 9042508.doc</td>
</tr>
</tbody>
</table>

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

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 H2-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 DRAFT LABELING _______ 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. DRAFT LABELING _______ 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 DRAFT LABELING _______” 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 DRAFT LABELING _______. 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
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-  

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

MAR 12 1999

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 H₂-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,

/LS/ 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