CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 019510/S026, 020249/S09

Trade Name: PEPCID INJECTION AND INJECTION PREMIXED

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: 019510/S026, 020249/S09

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
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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: 019510/S026, 020249/S09

APPROVAL LETTER

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 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) 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/ 3-17-99

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: 019510/S026, 020249/S09

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

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:

> "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 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 "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." 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. "Pepcid RPD Orally Disintegrating Tablets" has been added to the last paragraph of the ADVERSE REACTIONS section stating that "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." **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 "See PRECAITIONS, Pediatric Patients." 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 [i.e., from "...Storage)." to "...Storage.)"]. **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

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/ 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)

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)	MAR - 3 1999
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 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:

> "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 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

March 3, 1999
Concur.
/S/

cc:
NDA 19-462;
19-510;
19-527;
20-249;
20-752
HFD-180
HFD-180/LTalarico /S/ 3-3-99
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