CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-958/S015

Trade Name: Pepcid Complete chewable tablets

Generic Name: 10 mg famotidine, 800 mg calcium carbonate and 165 mg magnesium hydroxide

Sponsor: Merck & Co., Inc.

Approval Date: November 18, 2008

Purpose: Provides for the replacement of the current Pepcid Complete chewable tablet product with a new chewable tablet (EZ Chews) formulation and the introduction of a new “Tropical Fruit” flavor with associated packaging and labeling changes

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	
Statistical Review(s)	
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-958/S-015

Merck & Co., Inc.
Attention: Paulette Midgette
Manager, Regulatory Affairs
Worldwide OTC Regulatory Affairs
Sumneytown Pike, P.O. Box 4, UN-D129
West Point, PA 19486

Dear Ms. Midgette:

Please refer to your supplemental new drug application for NDA 20-958 dated July 18, 2008, received July 18, 2008, submitted under section 505 (b) of the Federal Food, Drug, and Cosmetic Act for Pepcid Complete (10 mg famotidine, 800 mg calcium carbonate and 165 mg magnesium hydroxide) chewable Tablets.

We also acknowledge receipt of your submissions dated July 31, August 8, September 12 and 19, October 28 and 29 and November 5, 2008.

This supplemental new drug application provides for the replacement of the current Pepcid™ Complete chewable tablet product with a new chewable tablet (EZ Chews) formulation and the introduction of a new "Tropical Fruit" flavor with associated packaging and labeling changes.

We have completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed upon labeling text. Only the referenced labels and count sizes for the new chewable tablet formulation are approved for use under this application.

The final printed labeling (FPL) must be identical to the enclosed labeling (5-, and 8-count carton label and 25x1-count dispensit carton label and 1-ct trade pouch label for the tropical fruit flavor; 25- and 50-count bottle label and 1-count sample pouch label for the tropical fruit, berry and mint flavors; and 100-count bottle label for the berry flavor), and must be formatted in accordance with the requirements of 21 CFR 201.66.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate these submissions "**FPL for approved supplement NDA 20-958/S-015**." Approval of these submissions by FDA is not required before the labeling is used.

Per your November 12, 2008 commitment, we remind you that the prominence of the tamper resistance statement will be increased and the statement "The makers of Pepcid Complete do not

manufacture store brands" will be removed from the back carton label on all tropical fruit carton labels by July 2009. We also remind you that the "NEW TASTE" and "NEW FLAVOR" flags must be removed from the label and labeling, wherever it appears, after the first six months of marketing.

Marketing the product with FPL that is not identical to the approved labeling text and in the required format may render the product misbranded and an unapproved new drug.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20857

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

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Joel Schiffenbauer, M.D.
Deputy Director
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

Enclosure

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

/s/

Joel Schiffenbauer

11/18/2008 06:12:22 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

LABELING

(b) (4)

Drug Facts

Active ingredients (in each chewable tablet) — Purpose

Famotidine 10 mg.....Acid reducer
Calcium carbonate 800 mg.....Antacid
Magnesium hydroxide 165 mg.....Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness

Pepcid® + Antacid = Pepcid Complete®

The acid reducing benefits of Pepcid AC | The neutralizing benefits of antacids | Combined in a single chewable tablet

Acid Reducer * Antacid

Do not use if the carton or individual pouch is open or torn.

The makers of Pepcid® Complete do not manufacture store brands.

Drug Facts (continued)

- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

Other information

- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use

(b) (4)

Ctn Pepcid Complete Fruit Chew Tab 5 FDA
June 25, 2008

3008793 D-2

(b) (4)

Drug Facts (continued)

- keep the carton. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, FD&C yellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments?
1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn

- Do not lie flat or bend over after eating
- Do not wear tight-fitting clothing around the stomach
- Do not eat before bedtime
- Raise the head of your bed
- Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables
- Eat slowly and avoid big meals
- If overweight, lose weight
- Quit smoking

The makers of Pepcid® Complete do not manufacture store brands

Pepcid® Complete is eligible for coverage by Flexible Spending Account dollars. See your employer for details.

Distributed by:

CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA
® Registered trademark of Merck & Co Inc
Please visit our website at: www.pepcidac.com

XXXXXXX

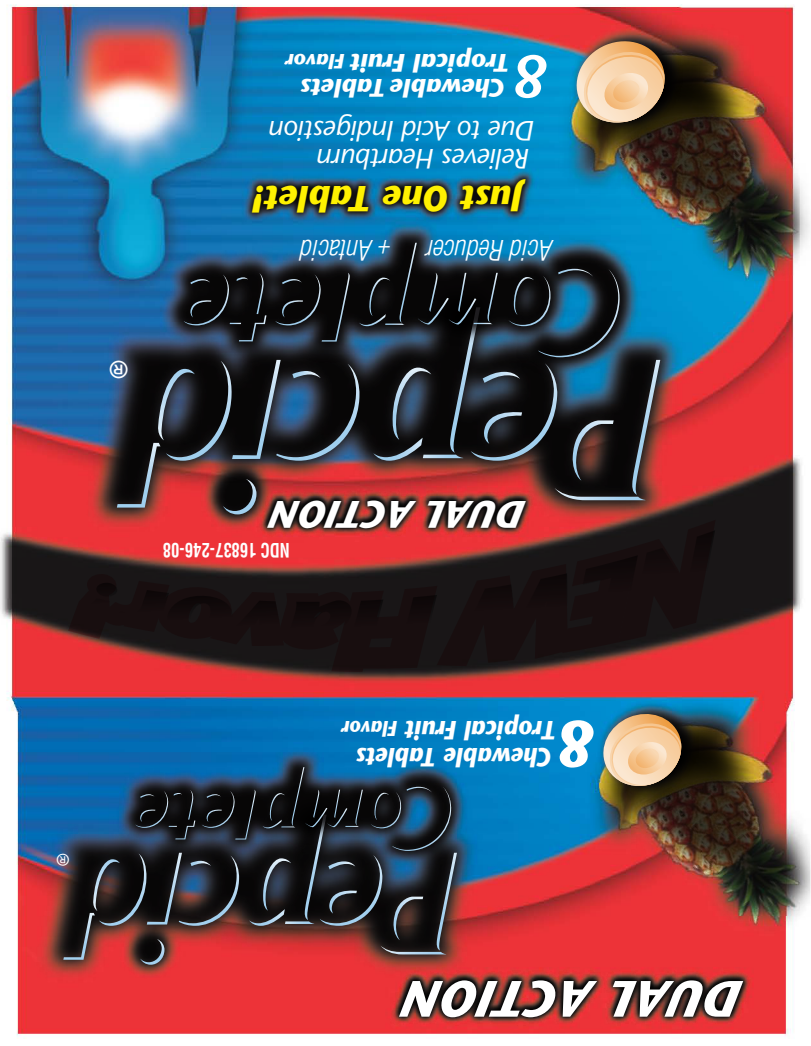
00000000

00000000

(b) (4)

Ctn Pepcid Complete Fruit Chew Tab 8 FDA 3008793 C-3
June 25, 2008

00000000



00000000

XXXXXX

Pepcid Complete®

Acid Reducer + Antacid

Pepcid + = Pepcid Complete

The acid reducing benefits of Pepcid AC

The neutralizing benefits of antacids

Combined in a single chewable tablet

Do not use if the carton or individual pouch is open or torn.

The makers of Pepcid® Complete do not manufacture store brands.

The makers of Pepcid® Complete do not manufacture store brands.

Drug Facts

Active ingredients (in each chewable tablet) ***Purpose***

Famotidine 10 mg.....Acid reducer
Calcium carbonate 800 mg.....Antacid
Magnesium hydroxide 165 mg.....Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use

- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if

- your heartburn continues or worsens
- you need to take this product for more than 14 days

Drug Facts (continued)

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

Other information

- each tablet contains: **calcium 320 mg; magnesium 70 mg**

Drug Facts (continued)

- read the directions and warnings before use
- keep the carton. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, FD&C yellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments?

1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

00000000

FPO

xxxxxxx

Do not use if pouch is open or torn.

Pepcid® + = Pepcid Complete®

The acid reducing benefits of Pepcid AC | The neutralizing benefits of antacids | Combined in a single chewable tablet

Acid Reducer + Antacid

The makers of Pepcid® Complete do not manufacture store brands.

Drug Facts

Active ingredients (in each chewable tablet)	Purpose
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions

- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

Other information

- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- keep the carton. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, FD&C yellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments? **1-800-755-4008** (English) or **1-888-466-8746** (Spanish)

WHAT YOU SHOULD KNOW ABOUT: ®

Acid Reducer + Antacid

PEPCID® COMPLETE combines an acid reducer (famotidine) with antacids (calcium carbonate and magnesium hydroxide) to relieve heartburn in two different ways: Acid reducers decrease the production of new stomach acid; antacids neutralize acid that is already in the stomach. The active ingredients in PEPCID® COMPLETE have been used for years to treat acid-related problems in millions of people safely and effectively.

Shown actual size

- **Just 1 tablet** relieves heartburn due to acid indigestion.

Use PEPCID® COMPLETE to relieve heartburn due to acid indigestion and sour stomach. Children under 12 years: ask a doctor

TO RELIEVE SYMPTOMS Chew **1 tablet** completely before swallowing.

PEPCID® COMPLETE can be used up to twice daily (up to 2 chewable tablets in 24 hours).

It is normal for the stomach to produce acid, especially after consuming food and beverages. However, acid in the stomach may move up into the wrong place (the esophagus), causing burning pain and discomfort that interfere with everyday activities.

• Heartburn—Caused by acid in the esophagus

A valve-like muscle called the lower esophageal sphincter (LES) is relaxed in an open position

Burning pain/ discomfort in esophagus

Acid moves up from stomach

Tips for Managing Heartburn
- Do not lie flat or bend over soon after eating.
- Do not eat late at night, or just before bedtime.
- Certain foods or drinks are more likely to cause heartburn, such as rich, spicy, fatty, and fried foods, chocolate, caffeine, alcohol, and even some fru ts and vegetables.
- Eat slowly and do not eat big meals.
- If you are overweight, lose weight.
- If you smoke, quit smoking.
- Raise the head of your bed.
- Wear loose fitting clothing around your stomach.

WHAT YOU SHOULD KNOW ABOUT: ®

Acid Reducer + Antacid

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Please call 1-800-755-4008 (English) or 1-888-466-8746 (Spanish) for more information and a guide on how to help control heartburn.

Pepcid® Complete is eligible for coverage by Flexible Spending Account dollars. See your employer for details.

The Pepcid® Complete Brand name is a guarantee of our commitment to you. We have worked hard to earn your trust and we'll work even harder to maintain it.

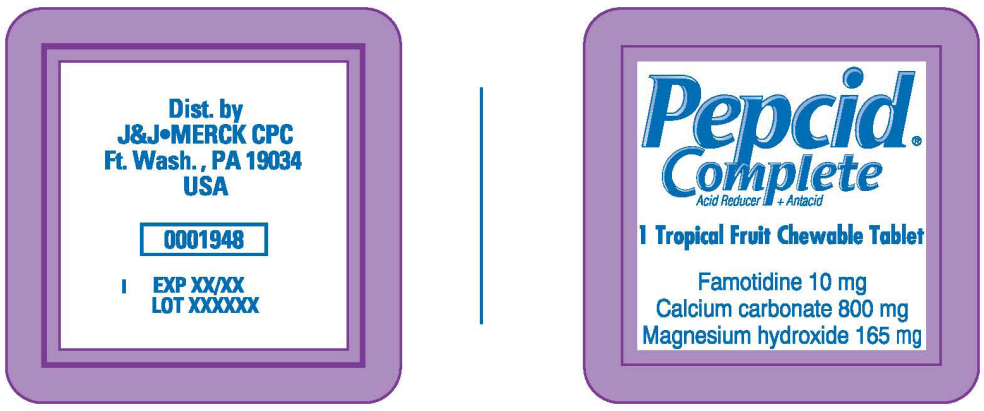
Distributed by:
CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
® Registered trademark of Merck & Co., Inc.
Please visit our website at: www.pepcidac.com

FPO

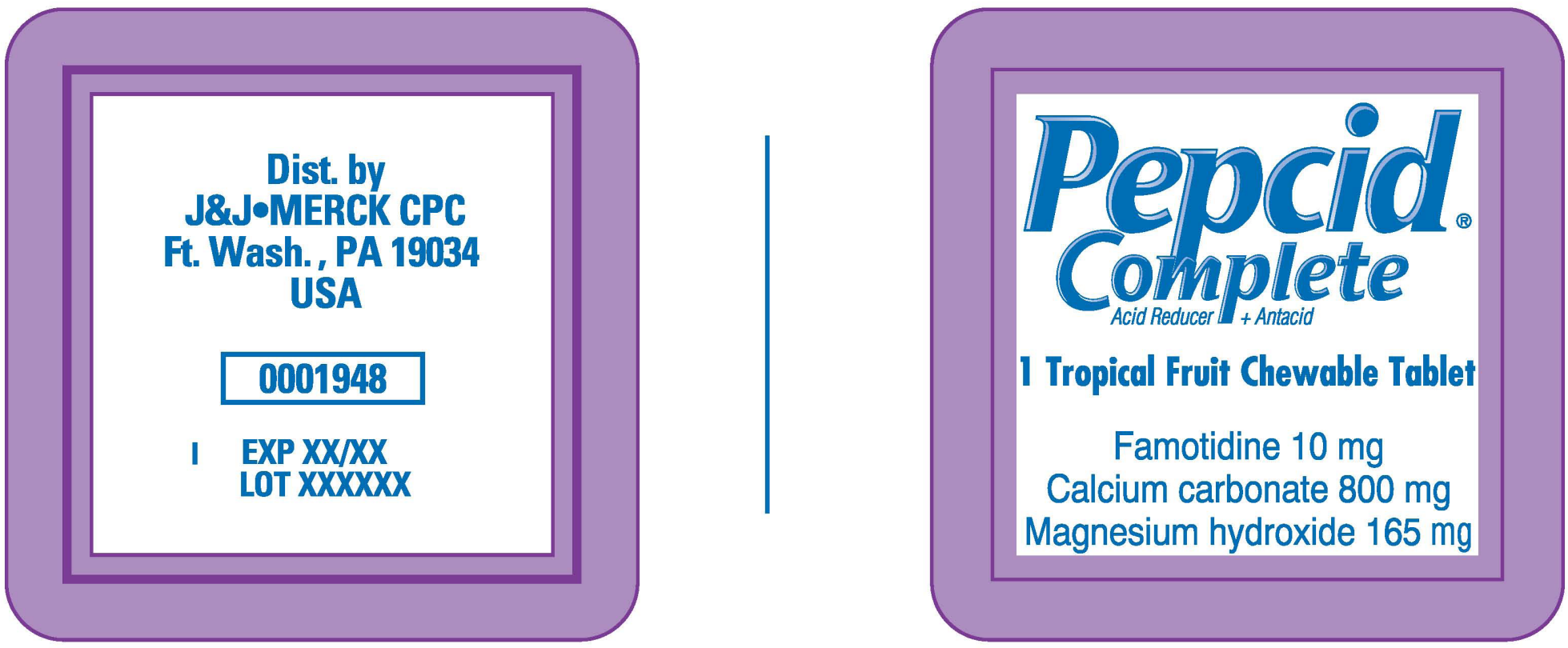
(b) (4)

(b) (4)

Blister @ 100% Scale



Blister @ 200% Scale



(b) (4)

LOT

EXP.

XXXXXXX

Drug Facts (continued)

Directions

- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

Other information

- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- read the bottle label. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients

cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, FD&C yellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake,

Drug Facts (continued)

flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments?

1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn

- Do not lie flat or bend over after eating
- Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime
- Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight
- Quit smoking

Shown actual size

XXXXXXX

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

The makers of Pepcid® Complete do not manufacture store brands.

Distributed by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA

® Registered trademark of Merck & Co., Inc.

Drug Facts (continued)

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use

- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**

Drug Facts (continued)

- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if

- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

(b) (4)

LOT

EXP.

XXXXXXX

Drug Facts (continued)

Directions

- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

Other information

- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- read the bottle label. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients

cellulose acetate, corn starch, crospovidone, D&C red #7 calcium lake, dextrose, FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake,

Drug Facts (continued)

flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments?

1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn

- Do not lie flat or bend over after eating
- Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime
- Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight
- Quit smoking

Shown actual size

XXXXXXX

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

The makers of Pepcid® Complete do not manufacture store brands.

Distributed by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA

® Registered trademark of Merck & Co., Inc.

Drug Facts (continued)

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use

- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

Ask a doctor before use if you have

- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**

Drug Facts (continued)

- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if

- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

(b) (4)

LOT

EXP.

XXXXXXX

Drug Facts (continued)

Directions

• adults and children 12 years and over:
  • **do not swallow tablet whole: chew completely**
  • to relieve symptoms, **chew** 1 tablet before swallowing
  • do not use more than 2 chewable tablets in 24 hours
• children under 12 years: ask a doctor

Other information

• each tablet contains: **calcium 320 mg; magnesium 70 mg**
• read the directions and warnings before use
• read the bottle label. It contains important information.
• store at 20°-30°C (68°-86°F)
• protect from moisture

Inactive ingredients

cellulose acetate, corn starch, crospovidone, D&C yellow #10 aluminum lake, dextrose, FD&C blue #1 aluminum lake, flavors, gum arabic,

Drug Facts (continued)

hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments?

1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn

• Do not lie flat or bend over after eating • Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime • Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight • Quit smoking

Shown actual size

XXXXXXX

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

The makers of Pepcid® Complete do not manufacture store brands.

Distributed by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA

® Registered trademark of Merck & Co., Inc.

Drug Facts (continued)

Warnings

Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use

• if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
• with other acid reducers

Ask a doctor before use if you have

• had heartburn over 3 months. This may be a sign of a more serious condition.
• heartburn with **lightheadedness, sweating, or dizziness**
• chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
• frequent **chest pain**

Drug Facts (continued)

• frequent wheezing, particularly with heartburn
• unexplained weight loss
• nausea or vomiting
• stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if

• your heartburn continues or worsens
• you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

(b) (4)

Drug Facts (continued)

Other information
- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- read the bottle label. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients
cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, FD&C yellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments?
1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

LOT

EXP.

XXXXXXX

Tips for Managing Heartburn
• Do not lie flat or bend over after eating • Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime • Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight • Quit smoking

Shown actual size

Distributed by:

CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA
® Registered trademark of Merck & Co., Inc.

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings
Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

The makers of Pepcid® Complete do not manufacture store brands.

Drug Facts (continued)

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

XXXXXXX

(b) (4)

Drug Facts (continued)

Other information
- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- read the bottle label. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients
cellulose acetate, corn starch, crospovidone, D&C red #7 calcium lake, dextrose, FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments?
1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn
• Do not lie flat or bend over after eating • Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime • Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight • Quit smoking

Shown actual size

Distributed by:

CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA
® Registered trademark of Merck & Co., Inc.

LOT

EXP.

XXXXXXX

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings
Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

The makers of Pepcid® Complete do not manufacture store brands.

Drug Facts (continued)

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

XXXXXXX

(b) (4)

Drug Facts (continued)

Other information
- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- read the bottle label. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients
cellulose acetate, corn starch, crospovidone, D&C yellow #10 aluminum lake, dextrose, FD&C blue #1 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments?
1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn
• Do not lie flat or bend over after eating • Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime • Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight • Quit smoking

Shown actual size

Distributed by:

CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA
® Registered trademark of Merck & Co., Inc.

LOT

EXP.

XXXXXXX

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings
Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

The makers of Pepcid® Complete do not manufacture store brands.

Drug Facts (continued)

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

XXXXXXX

(b) (4)

Do not use if pouch is open or torn.

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use: relieves heartburn associated with acid indigestion and sour stomach

Warnings: **Allergy alert:** Do not use if you are allergic to famotidine or other acid reducers

Do not use • if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor. • with other acid reducers. **Ask a doctor before use if you have** • had heartburn over 3 months. This may be a sign of a more serious condition. • heartburn with **lightheadedness, sweating, or dizziness** • chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness • frequent **chest pain** • frequent wheezing, particularly with heartburn • unexplained weight loss • nausea or vomiting • stomach pain. **Ask a doctor or pharmacist before use if you are** presently taking a prescription drug. Antacids may interact with certain prescription drugs. **Stop use and ask a doctor if** • your heartburn continues or worsens • you need to take this product for more than 14 days. **If pregnant or breast-feeding,** ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away. ***Directions*** • adults and children 12 years and over: • **do not swallow tablet whole: chew completely** • to relieve symptoms, **chew** 1 tablet before swallowing • do not use more than 2 chewable tablets in 24 hours • children under 12 years: ask a doctor. ***Other information*** • each tablet contains: **calcium 320 mg; magnesium 70 mg** • read the directions and warnings before use • store at 20-30 C (68-86 F) • protect from moisture. ***Inactive ingredients*** cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, FD&C yellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments? **1-800-755-4008** (English) or **1-888-466-8746** (Spanish)

Dist. by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
®Registered trademark of Merck & Co., Inc. www.pepcidac.com XXXXXXX

150% OF SIZE

Do not use if pouch is open or torn.

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use: relieves heartburn associated wi h acid indigestion and sour stomach

Warnings: **Allergy alert:** Do not use if you are allergic to famotidine or o her acid reducers

Do not use • if you have trouble or pain swallowing food, vomiting wi h blood, or bloody or black stools. These may be signs of a serious condition. See your doctor. • wi h o her acid reducers. **Ask a doctor before use if you have** • had heartburn over 3 mon hs. This may be a sign of a more serious condition. • heartburn wi h **lightheadedness, sweating, or dizziness** • chest pain or shoulder pain wi h shortness of brea h; sweating; pain spreading to arms, neck or shoulders; or ligh headedness • frequent **chest pain** • frequent wheezing particularly wi h heartburn • une plained weight loss • nausea or omiting • stomach pain. **Ask a doctor or pharmacist before use f you are** presently taking a prescription drug. Antacids may interact wi h certain prescription drugs. **Stop use and ask a doctor if** • your heartburn continues or worsens • you need to take his product for more han 14 days. **If pregnant or breast-feeding,** ask a heal h professional before use. **Keep out of reach of children.** In case of o erdose get medical help or contact a Poison Control Center right away. ***Directions*** • adults and chi dren 12 years and o er: • **do not swallow tablet whole: chew completely** • to relieve symptoms, **chew** 1 tablet before swallowing • do not use more han 2 chewable tablets in 24 hours • children under 12 years: ask a doctor. ***Other information*** • each tablet contains: **calcium 320 mg; magnesium 70 mg** • read he directions and warnings before use • store at 20-30 C (68-86 F) • protect from moisture. ***Inactive ingredients*** cellulose acetate, corn starch, corn syrup solids, crospovidone, dextrose, D&C ellow #5 aluminum lake (tartrazine), FD&C yellow #6 aluminum lake, flavors, gum arabic, hydrox propyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose, triacetin

Questions or comments? **1-800-755 4008** (English) or **1-888-466-8746** (Spanish)

Dist. by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
®Registered trademark of Merck & Co., Inc. www pepcidac com XXXXXXX

(b) (4)

Pouch Pepcid Complete Fruit Chew Tab FDA 3008793 F-2
June 25, 2008

Do not use if pouch is open or torn.

Active ingredients (in each chewable tablet)	*Purpose*
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use: relieves heartburn associated with acid indigestion and sour stomach

Warnings: **Allergy alert:** Do not use if you are allergic to famotidine or other acid reducers

Do not use • if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor. • with other acid reducers. **Ask a doctor before use if you have** • had heartburn over 3 months. This may be a sign of a more serious condition. • heartburn with **lightheadedness, sweating, or dizziness** • chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness • frequent **chest pain** • frequent wheezing, particularly with heartburn • unexplained weight loss • nausea or vomiting • stomach pain. **Ask a doctor or pharmacist before use if you are** presently taking a prescription drug. Antacids may interact with certain prescription drugs. **Stop use and ask a doctor if** • your heartburn continues or worsens • you need to take this product for more than 14 days. **If pregnant or breast-feeding,** ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

Directions • adults and children 12 years and over: • **do not swallow tablet whole: chew completely** • to relieve symptoms, **chew** 1 tablet before swallowing • do not use more than 2 chewable tablets in 24 hours • children under 12 years: ask a doctor. ***Other information*** • each tablet contains: **calcium 320 mg; magnesium 70 mg** • read the directions and warnings before use • store at 20-30 C (68-86 F) • protect from moisture. ***Inactive ingredients*** cellulose acetate, corn starch, crospovidone, D&C red 7 calcium lake, dextrose, FD&C blue 1 aluminum lake, FD&C red 40 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments? **1-800-755-4008** (English) or **1-888-466-8746** (Spanish)

Dist. by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
®Registered trademark of Merck & Co., Inc. www.pepcidac.com XXXXXXX

150% OF SIZE

Do not use if pouch is open or torn.

Active ingredients (in each chewable tablet)	*Purpose*
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use: relieves heartburn associated with acid indigestion and sour stomach

Warnings: **Allergy alert:** Do not use if you are allergic to famotidine or other acid reducers

Do not use • if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor. • with other acid reducers. **Ask a doctor before use if you have** • had heartburn over 3 months. This may be a sign of a more serious condition. • heartburn with **lightheadedness, sweating, or dizziness** • chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness • frequent **chest pain** • frequent wheezing, particularly with heartburn • unexplained weight loss • nausea or vomiting • stomach pain. **Ask a doctor or pharmacist before use if you are** presently taking a prescription drug. Antacids may interact with certain prescription drugs. **Stop use and ask a doctor if** • your heartburn continues or worsens • you need to take this product for more than 14 days. **If pregnant or breast-feeding,** ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

Directions • adults and children 12 years and over: • **do not swallow tablet whole: chew completely** • to relieve symptoms, **chew** 1 tablet before swallowing • do not use more than 2 chewable tablets in 24 hours • children under 12 years: ask a doctor. ***Other information*** • each tablet contains: **calcium 320 mg; magnesium 70 mg** • read the directions and warnings before use • store at 20-30 C (68-86 F) • protect from moisture. ***Inactive ingredients*** cellulose acetate, corn starch, crospovidone, D&C red 7 calcium lake, dextrose, FD&C blue 1 aluminum lake, FD&C red 40 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments? **1-800-755-4008** (English) or **1-888-466-8746** (Spanish)

Dist. by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
®Registered trademark of Merck & Co., Inc. www.pepcidac.com XXXXXXX

(b) (4)

Pouch Pepcid Complete Berry Chew Tab 1 FDA ***3008957 A-1***
October 23, 2008

Do not use if pouch is open or torn.

Active ingredients (in each chewable tablet) ***Purpose***

Famotidine 10 mg..... Acid reducer
Calcium carbonate 800 mg..... Antacid
Magnesium hydroxide 165 mg..... Antacid

Use: relieves heartburn associated with acid indigestion and sour stomach

Warnings: **Allergy alert:** Do not use if you are allergic to famotidine or other acid reducers

Do not use • if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor. • with other acid reducers. **Ask a doctor before use if you have** • had heartburn over 3 months. This may be a sign of a more serious condition. • heartburn with **lightheadedness, sweating, or dizziness** • chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness • frequent **chest pain** • frequent wheezing, particularly with heartburn • unexplained weight loss • nausea or vomiting • stomach pain. **Ask a doctor or pharmacist before use if you are** presently taking a prescription drug. Antacids may interact with certain prescription drugs. **Stop use and ask a doctor if** • your heartburn continues or worsens • you need to take this product for more than 14 days. **If pregnant or breast-feeding,** ask a health professional before use. **Keep out of reach of children.** In case of overdose, get medical help or contact a Poison Control Center right away.

Directions • adults and children 12 years and over: • **do not swallow tablet whole: chew completely** • to relieve symptoms, **chew** 1 tablet before swallowing • do not use more than 2 chewable tablets in 24 hours • children under 12 years: ask a doctor

Other information • each tablet contains: **calcium 320 mg; magnesium 70 mg** • read the directions and warnings before use • store at 20-30 C (68-86 F) • protect from moisture

Inactive ingredients cellulose acetate, corn starch, crospovidone, D&C yellow 10 aluminum lake, dextrose, FD&C blue 1 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments? **1-800-755-4008** (English) or **1-888-466-8746** (Spanish)

Dist. by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
®Registered trademark of Merck & Co., Inc. www.pepcidac.com XXXXXXX

150% OF SIZE

Do not use if pouch is open or torn.

Active ingredients (in each chewable tablet) ***Purpose***

Famotidine 10 mg..... Acid reducer
Calcium carbonate 800 mg..... Antacid
Magnesium hydroxide 165 mg..... Antacid

Use: relieves heartburn associated wi h acid indigestion and sour stomach

Warnings: **Allergy alert:** Do not use if you are allergic to famotidine or o her acid reducers

Do not use • if you ha e trouble or pain swallowing food, omiting wi h blood, or bloody or black stools. These may be signs of a serious condition. See your doctor. • wi h o her acid reducers. **Ask a doctor before use if you have** • had heartburn o er 3 mon hs. This may be a sign of a more serious condition. • heartburn wi h **lightheadedness, sweating, or dizziness** • chest pain or shou der pain wi h shortness of brea h; sweating; pain spreading to arms, neck or shou ders; or ligh headedness • frequent **chest pain** • frequent wheezing particularly wi h heartburn • une plained weight loss • nausea or omiting • stomach pain. **Ask a doctor or pharmacist before use f you are** presently taking a prescription drug. Antacids may interact wi h certain prescription drugs. **Stop use and ask a doctor if** • your heartburn continues or worsens • you need to take his product for more han 14 days. **If pregnant or breast-feeding,** ask a hea h professional before use. **Keep out of reach of children.** In case of o erdose, get medica help or contact a Poison Control Center right away.

Directions • adu ts and chi dren 12 years and over: • **do not swallow tablet whole: chew completely** • to relieve symptoms, **chew** 1 tablet before swallowing • do not use more han 2 chewable tablets in 24 hours • chi dren under 12 years: ask a doctor

Other information • each tablet contains: **calcium 320 mg; magnesium 70 mg** • read he directions and warnings before use • store at 20-30 C (68- 6 F) • protect from moisture

Inactive ingredients cellulose acetate, corn starch, crospovidone, D&C ellow 10 aluminum lake, dextrose, FD&C blue 1 aluminum lake, flavors gum arabic, hydroxypropyl cellulose, h promellose, lactose, magnesium stearate, ma todextrin, mineral oil, sucralose

Questions or comments? **1-800-755-4008** (English) or **1-888 466-8746** (Spanish)

Dist. by:

CONSUMER PHARMACEUTICALS CO., FORT WASHINGTON, PA 19034 USA
®Registered trademark of Merck & Co., Inc. www pepcidac com XXXXXXX

(b) (4)

Pouch Pepcid Complete Cool Mint Chew Tab 1 FDA ***3008958 A-1***
October 23, 2008

Drug Facts (continued)

Other information
- each tablet contains: **calcium 320 mg; magnesium 70 mg**
- read the directions and warnings before use
- read the bottle label. It contains important information.
- store at 20°-30°C (68°-86°F)
- protect from moisture

Inactive ingredients
cellulose acetate, corn starch, crospovidone, D&C red #7 calcium lake, dextrose, FD&C blue #1 aluminum lake, FD&C red #40 aluminum lake, flavors, gum arabic, hydroxypropyl cellulose, hypromellose, lactose, magnesium stearate, maltodextrin, mineral oil, sucralose

Questions or comments?
1-800-755-4008 (English) or **1-888-466-8746** (Spanish)

Tips for Managing Heartburn
• Do not lie flat or bend over after eating • Do not wear tight-fitting clothing around the stomach • Do not eat before bedtime • Raise the head of your bed • Avoid heartburn-causing foods such as rich, spicy, fatty or fried foods, chocolate, caffeine, alcohol, and certain fruits and vegetables • Eat slowly and avoid big meals • If overweight, lose weight • Quit smoking

Shown actual size

Distributed by:

CONSUMER PHARMACEUTICALS CO.
FORT WASHINGTON, PA 19034 USA
® Registered trademark of Merck & Co., Inc.

LOT

EXP.

XXXXXXX

For Complete Directions and Warnings

DO NOT USE IF PRINTED FOIL SEAL UNDER BOTTLE CAP IS OPEN OR TORN.

Drug Facts

Active ingredients (in each chewable tablet)	***Purpose***
Famotidine 10 mg	Acid reducer
Calcium carbonate 800 mg	Antacid
Magnesium hydroxide 165 mg	Antacid

Use relieves heartburn associated with acid indigestion and sour stomach

Warnings
Allergy alert: Do not use if you are allergic to famotidine or other acid reducers

Do not use
- if you have trouble or pain swallowing food, vomiting with blood, or bloody or black stools. These may be signs of a serious condition. See your doctor.
- with other acid reducers

®

Drug Facts (continued)

Ask a doctor before use if you have
- had heartburn over 3 months. This may be a sign of a more serious condition.
- heartburn with **lightheadedness, sweating, or dizziness**
- chest pain or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or lightheadedness
- frequent **chest pain**
- frequent wheezing, particularly with heartburn
- unexplained weight loss
- nausea or vomiting
- stomach pain

Ask a doctor or pharmacist before use if you are presently taking a prescription drug. Antacids may interact with certain prescription drugs.

Stop use and ask a doctor if
- your heartburn continues or worsens
- you need to take this product for more than 14 days

If pregnant or breast-feeding, ask a health professional before use.
Keep out of reach of children. In case of overdose, get medical help or contact a Poison Control Center right away.

Directions
- adults and children 12 years and over:
  - **do not swallow tablet whole: chew completely**
  - to relieve symptoms, **chew** 1 tablet before swallowing
  - do not use more than 2 chewable tablets in 24 hours
- children under 12 years: ask a doctor

XXXXXXX

(b) (4)

Lbl Pepcid Complete Berry Chew Tab 100 FDA October 23, 2008 ***3008791 C-3***

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation (DNCE)

Date: October 20, 2008

From: Linda Hu, MD
Medical Officer, DNCE

Subject: NDA 20-958 (S-015), Pepcid Complete EZ Chewable Tablets
Famotidine 10 mg/ Calcium carbonate 800 mg/Magnesium hydroxide 165 mg

Sponsor: Johnson & Johnson -- Merck Consumer Pharmaceuticals Co.

PDUFA: November 18, 2008

1 Introduction and Regulatory Background

Famotidine single ingredient and combination products are marketed over-the-counter (OTC) for prevention and treatment of heartburn. Pepcid AC (famotidine 10 mg) and Maximum Strength Pepcid AC (famotidine 20 mg), have been available without a prescription for the prevention and treatment of heartburn since 1995 and 2003 respectively. A famotidine with antacid combination product, Pepcid Complete (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg) has been available OTC since 2000. Johnson & Johnson – Merck Consumer Pharmaceuticals Co. (JJMCPC) would like to modify the currently approved Pepcid Complete Chewable Tablets formulation and replace it in the marketplace with a softer chewable tablet (EZ Chews).

JJMCPC is filing a prior approval supplement to NDA 20-958 for Pepcid Complete chewable tablets (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg, approved 10/16/00). An FDA/Sponsor teleconference was held on Oct 24, 2007 to discuss the Sponsor's plan to file this supplement. Merck felt that a bioequivalence study would not be required to support the approval of this product. The Agency stated that the proposed formulation changes are considered a Level 3 Scale-Up and Postapproval Change (SUPAC) and, as such, would generate a recommendation for a bioequivalence study. The Sponsor proposed to use the current Pepcid Complete product (b) (4) as the reference standard, compared to the new formulation (b) (4) in the clinical testing. The Agency stated that Pepcid Complete would be the appropriate reference standard and that the supplemental application would qualify for a prior

approval supplement with a 4-month review clock. The Sponsor was also informed that if the proposed formulation was not bioequivalent to the reference formulation, then appropriate safety or efficacy data would need to be provided. In addition, Acid Neutral Capacity equivalence data would be required for this application.

1.1 Product Information

Famotidine is a competitive, reversible inhibitor of histamine action at the H2 receptor. Nonprescription famotidine FCT (film-coated tablet) was approved in the United States in 1995 at the 10 mg strength and in 2003 at the 20 mg strength for the short-term treatment of heartburn, acid indigestion and sour stomach, and for the prevention of these symptoms brought on by consuming food and beverages that are known to cause these symptoms. It is also approved for prescription use in many countries for treatment of active duodenal ulcer and gastric ulcer, for maintenance therapy of duodenal ulcer disease, for GERD, and for long-term management of Zollinger-Ellison syndrome. Doses up to 160 mg q 6 hour have been administered to some adult patients with severe Zollinger-Ellison Syndrome. Over 10,000 patients have received famotidine in controlled trials performed worldwide. Side effects have generally been mild and have included headache, constipation, diarrhea, and dizziness.

Antacids have also been a standard of therapy for nonprescription treatment of acid-related symptoms. Antacids are believed to work rapidly by neutralizing intraluminal acid on contact. Pharmacodynamic data with antacids suggest that the duration of the antacid effect may be ~2 hours in the esophagus and may depend on excipients. The duration of action may also be limited by physiologic clearing mechanisms like gastric and/or esophageal emptying. This limited duration of action may result in the need for frequent re-dosing in order to control symptoms.

A fixed combination of famotidine and antacid provides the benefits of more rapid relief of symptoms than famotidine alone, and a longer duration of relief than antacid alone. Pepcid Complete, a chewable tablet containing famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg is currently approved in the United States as well as many other countries for treatment of acid indigestion, heartburn, sour stomach and associated symptoms of upset stomach. The antacid component of this tablet provided 21 mEq of acid-neutralizing capacity (ANC). This antacid dose is within the range of doses typically used in OTC antacid products for treatment of intermittent heartburn (11 to 55 mEq).

To provide an alternative tablet formulation for consumers, JJMCPC has developed a softer chewable tablet (EZ Chews formulation) of famotidine + antacid. The amount of active ingredient in the new formulation will not change from the currently approved product (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg). According to the Sponsor, (b) (4) .

2 Chemistry

The antacid component of this tablet provides21 mEq of acid-neutralizing capacity (ANC). This antacid dose is within the range of doses typically used in OTC antacid products for treatment of intermittent heartburn (11 to 55 mEq).

See the chemistry review for further detail and comments on the chemistry data in this submission.

3 Clinical Pharmacology

The Sponsor submitted one clinical trial in support of this application, Study 145 titled "A Single-Dose, Open-Label, Three-Period Crossover Study to Assess the Bioequivalence of Famotidine/Antacid Combination Tablets (FACT) Compared to Famotidine/Antacid EZ Chew Tablet Without Water and Famotidine/Antacid EZ Chew Tablet With Water."

Study 145 was submitted to show bioequivalence of the new formulation to the approved formulation of famotidine-antacid combination tablets. This study used a three-period, randomized, crossover design, where each subject received 3 treatments: the reference product FACT; famotidine/antacid combination EZ Chew Tablet (EZ Chew) without water and EZ Chew with water. The duration of the entire study was approximately 6 weeks.

For bioequivalence evaluations, plasma concentrations of famotidine were used to calculate pharmacokinetic parameters including AUC and C_{max} for each subject following single dose administration of FACT with water, EZ Chew without water and EZ Chew with water. Safety and tolerability were assessed by pre-study and post-study physical examinations and monitoring for adverse experiences.

Primary Objective: To assess the bioequivalence of a single dose of EZ Chew taken *without* water compared with a single dose of FACT taken with water. The hypothesis is that the plasma AUC and C_{max} of a single dose of EZ Chew *without* water are equivalent to those of a single dose of FACT with water. That is, the geometric mean AUC and C_{max} ratios (EZ Chew without water/FACT with water) are within the interval of 0.80 and 1.25.

Secondary Objective: To assess the bioequivalence of a single dose of EZ Chew taken *with* water compared with a single dose of FACT taken with water. The hypothesis is that the plasma AUC and C_{max} of a single dose of EZ Chew *with* water are equivalent to those of a single dose of FACT with water. That is, the geometric mean AUC and C_{max} ratios (EZ Chew without water/FACT with water) are within the interval of 0.80 and 1.25.

Procedure: For this open-label, single-dose, three-period crossover study, 24 healthy subjects were randomized to 1 of 6 treatment sequences. Subjects participated in all three treatment periods. FACT was administered with 120 mL of water. The EZ Chew was administered without water for one treatment period and with water for one treatment period. Each treatment period was separated by a 5 to 7 day washout period.

Subjects were sequestered in the study unit on the evening prior to treatment. Following an overnight fast (NPO after midnight), subjects received the designated treatment between 6 AM and 9 AM. Subjects were provided with a light meal after the 4-hour blood sample. Blood was collected over 24 hours post-dose for measurement of famotidine concentrations. The 5 to 7 day washout began at the 24-hour sample. Subjects remained in the study unit until the 24- hour blood collection was completed.

Physical examinations (including vital signs) and laboratory tests were performed. Laboratory safety evaluations on blood and urine were performed on samples that were collected 2 to 3 weeks pre-study. These test values had to be normal or had to conform to protocol standards before subjects were enrolled. The completed laboratory screening tests were: (pre-study) hemoglobin, hematocrit, WBC (total and differential), platelet count; ALT, AST, alkaline phosphatase, total bilirubin, sodium, potassium, chloride, creatinine, total protein, CO_2, BUN, and albumin. Women participating in this study were tested for serum beta human chorionic gonadotropin (β-hCG) at screening and post-study, and a urine β-hCG test was done at the start of each treatment period.

The schedule of procedures was

Schedule of Clinical Observations and Laboratory Measurements

		Treatment Periods 1, 2, and 3‡																	
	Pre-study†	Predose	0 min	5 min	15 min	30 min	45 min	60 min	90 min	2 hr	2 ½ hr	3 hr	4 hr	6 hr	8 hr	10 hr	12 hr	14 hr	24 hr	Post study
Evaluation of inclusion/exclusion criteria	X																			
HIPAA and Informed Consent	X																			
Medical History	X																			
Physical Examination	X																			X
Laboratory Safety	X																			
Serum pregnancy for females	X																			X
Urine Pregnancy for females§		X																		
Plasma samples for assay		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
BP/HR		X						X											X	
Dosing			X																	
Monitor Adverse Experiences			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

† This visit is conducted approximately 3 weeks prior to the first treatment visit. This will allow for laboratory safety analyses on blood and urine to be conducted to ensure that the test values are normal before the volunteer is entered into the study.
‡ A 5 to 7 day washout period between treatment visits
§ Urine pregnancy test must be performed for females prior to dosing at each treatment visit.

Data Source: [16.1.1.1]

The randomization scheme was

Allocation of Subjects to Treatment

Treatment Sequence	Period 1	Period 2	Period 3
Treatment Sequence 1	FACT with 120 mL of water	EZ Chew without water	EZ Chew with 120 mL of water
Treatment Sequence 2	EZ Chew without water	EZ Chew with 120 mL of water	FACT with 120 mL of water
Treatment Sequence 3	EZ Chew with 120 mL of water	FACT with 120 mL of water	EZ Chew without water
Treatment Sequence 4	FACT with 120 mL of water	EZ Chew with 120 mL of water	EZ Chew without water
Treatment Sequence 5	EZ Chew without water	FACT with 120 mL of water	EZ Chew with 120 mL of water
Treatment Sequence 6	EZ Chew with 120 mL of water	EZ Chew without water	FACT with 120 mL of water

Inclusion Criteria were as follows:

- Subject was a healthy male or female. Females must not have been pregnant or lactating. Females of childbearing potential must have been using and planned to continue using reliable means of contraception (other than oral contraceptives) during the course of the study. (At least 8 of each gender must be enrolled.)
- Subject was between the ages of 18 and 45 years.
- Subject weighed between 60 and 90 kg or was within ±20% of ideal body weight (based on Metropolitan Life tables).
- Subject judged to be in good health based on medical history.
- Subject was able to abstain from smoking during the 24-hour periods before and during each day of treatment.
- Subject understood the procedures and agreed to participate in the study by providing written informed consent.

Exclusion Criteria were as follows:

- The subject's prestudy laboratory screen had clinically significant abnormality.
- Subject's prestudy physical examination had clinically significant result.
- Subject had any major systemic disorders including psychiatric, cardiac, hypertension, diabetes mellitus, renal, or hepatic disease.
- Subject had a history of duodenal ulcer, gastric ulcer, peptic ulcer disease, atrophic gastritis, diverticulitis, esophageal strictures, Barrett's esophagus, endoscopically identified erosive esophagitis of moderate or greater severity, Zollinger-Ellison syndrome, inflammatory bowel disease, known to have gallstones, or other gastrointestinal (GI) disease, or GI surgery other than appendectomy.
- Subject had an atopic condition, or previous history of asthma, or multiple and/or severe allergies to drugs or foods.
- Subject used prescribed or nonprescribed drugs on a regular basis (including recreational use of illicit drugs).

- Subject had a recent (within the last 3 years) history of drug and/or alcohol abuse.
- Subject had recently used (within 1 week of signing consent) sucralfate, nizatidine, cimetidine, ranitidine, famotidine, cisapride, metoclopramide, misoprostol, or any other medication which modifies acid secretion. In addition, recent use of nonsteroidal anti-inflammatory drugs (NSAID), orally administered corticosteroids, anticholinergics, anticoagulants, tranquilizers, tricyclic antidepressants, and antineoplastics were prohibited.
- Subject had recently used (within 4 weeks of first treatment visit) of omeprazole, lansoprazole, rabeprazole, pantoprazole, or esomeprazole.
- Administration of nicotine replacement therapy during the study. Smoking habits of the patient should have remained consistent throughout the study.
- Subject habitually consumed more than 6 cups of coffee per day.
- Subject had unconventional or extreme dietary habits.
- Subject had donated a unit of blood or had been involved in a clinical trial where he/she had received an investigational drug during the 30 days prior to the start of the study.
- Subject had a history of any illness that, in the opinion of the investigator, might have confounded the results of the study or posed additional risk in administering the study drugs to the subject.
- Subject was in a situation or had any condition, which in the investigator's opinion, may interfere with optimal participation in the study.
- Subject had history of allergy or intolerance to antacids, H2-receptor antagonists (including cimetidine, ranitidine, nizatidine, and famotidine), or any other component of the study drug.
- Known pregnancy or was not using reliable means of contraception.
- Study personnel and immediate relatives of study personnel were not permitted to participate.

MO Comment: The inclusion and exclusion criteria are standard and acceptable from the safety point of view.

Discontinuation of Subject From Therapy or Study Observation
Adverse experiences were monitored throughout the study. No subjects were discontinued due to an adverse experience or for any other reason.

Pharmacokinetic Results

Pharmacokinetic Parameters of $AUC_{0-\infty}$ and C_{max}
Summary of FACT Versus EZ Chew With and Without Water (N=24)

Pharmacokinetic Parameter	N	Geometric Mean			Geometric Mean Ratio		MSE
		(FACT) with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)	
$AUC_{0-\infty}$ (ng/mL hr)	24	248.0 (216.4, 284.2)	261.2 (227.9, 299.3)	260.1 (227.0, 298.0)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	0.022
C_{max} (ng/mL)	24	44.4 (38.1, 51.7)	45.5 (39.1, 52.9)	45.9 (39.4, 53.4)	1.03 (0.93, 1.13)	1.03 (0.93, 1.14)	0.044

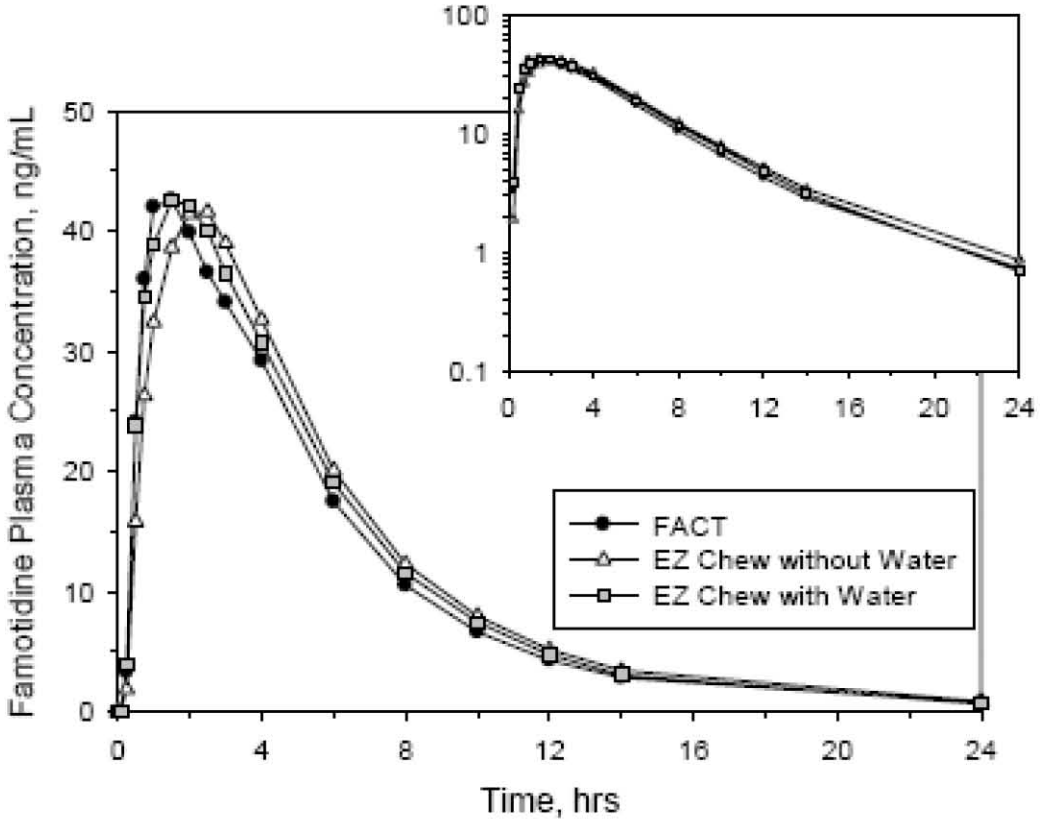
Geometric Means based on least square estimates from an ANOVA performed on natural log-transformed values
MSE=Mean Square Error on log scale
Test for Carryover Effect was non-significant: AUC p-value= 0.965, Cmax p-value= 0.980

Pharmacokinetic Parameters of T_{max} and Half-Life
Summary of FACT Versus EZ Chew With and Without Water (N=24)

Pharmacokinetic Parameter	N	Treatment Statistics			Median Treatment Differences	
		FACT with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)
T_{max} (hr)	24	1.25	1.75	1.50	0.50 (0.00, 0.75)	0.50 (0.00, 0.75)
Apparent Half-Life (hr)	24	4.60	4.56	4.16	-0.26 (-0.70, 0.32)	-0.58 (-1.12, -0.04)

Harmonic means are report for Half-Life treatment statistics. Medians are report for Tmax treatment statistics.
Median treatment differences and confidence intervals are based on Hodges-Lehmann estimates.

Arithmetic Mean Famotidine Plasma Concentration Profiles
Following Administration of Single Doses of
FACT with Water, EZ Chew without Water, and EZ Chew with Water
to Healthy Male and Female Subjects
(N=24/Treatment; Inset = Semilog Scale)



The statistical analyses of AUC and Cmax were conducted using an analysis of variance (ANOVA) model appropriate for a three-period crossover design. The ANOVA model contained factors for subject (random effect), period, treatment, and within-subject error. Treatment groups were compared using 90% confidence intervals for the difference in means for log-transformed values. These confidence intervals were calculated using the mean square error (MSE) from the ANOVA (referencing a t-distribution) and were exponentiated to obtain the 90% confidence interval for the true geometric mean ratios.

The pharmacokinetics results were as follows: All 24 subjects who entered and completed the 3 study periods were included in the analyses. The 90% CI for the geometric mean ratios (EZ Chew without water/FACT) for AUC was (0.98, 1.13). Since this interval is contained within the range (0.80, 1.25), famotidine/antacid combination EZ Chew without water and FACT with

water are considered bioequivalent with respect to AUC. The 2 treatments are also bioequivalent with respect to C_{max} based on the 90% CI of (0.93, 1.13). The median T_{max} was 1.75 hours for the EZ Chew without water and 1.25 hours for FACT and the median apparent half-life was 4.56 and 4.60 hours respectively. The 90% CI for the geometric mean ratio (EZ Chew with water/FACT) for AUC was (0.98, 1.13). Since this interval falls within the range (0.80, 1.25), famotidine EZ Chew with water and FACT with water are considered bioequivalent with respect to AUC. The 2 products are also bioequivalent with respect to Cmax based on the 90% CI of (0.93, 1.14). The median T_{max} was 1.50 hours for EZ Chew with water, compared to 1.25 hours for FACT. The medians for apparent half-life were 4.16 hours for EZ Chew with water and 4.60 hours for FACT).

Safety Evaluation

In the bioequivalence study (Study 145), seven subjects reported clinical adverse experiences. One of the subjects reported clinical adverse experiences that were determined by the investigator to be probably related to study drug and two subjects reported clinical adverse experiences that were determined by the investigator to be possibly related to study drug. None of the adverse experiences were serious and no subject withdrew from the study due to an adverse experience. All adverse experiences resolved. No new or unexpected adverse experiences were seen in this study and the adverse experience profile of this study was similar to what has been seen before in other famotidine studies. Famotidine/antacid combination was found to be generally safe and well tolerated.

Number (%) of Subjects with Specific Clinical Adverse Experiences by Body System and Treatment

	FACT	EZ	EZw	Total
	(N=24)	(N=24)	(N=24)	(N=24)
Number (%) of Subjects:	n %	n %	n %	n %
Subjects with one or more clinical adverse experiences	2 (8.3)	3 (12.5)	5 (20.8)	7 (29.2)
Subjects with no clinical adverse experience	22 (91.7)	21 (87.5)	19 (79.2)	17 (70.8)
Gastrointestinal disorders	1 (4.2)	1 (4.2)	0 (0.0)	2 (8.3)
Flatulence	1 (4.2)	0 (0.0)	0 (0.0)	1 (4.2)
Stomach Discomfort	0 (0.0)	1 (4.2)	0 (0.0)	1 (4.2)
Nervous system disorders	1 (4.2)	2 (8.3)	5 (20.8)	6 (25.0)
Headache	1 (4.2)	2 (8.3)	4 (16.7)	5 (20.8)
Syncope vasovagal	0 (0.0)	0 (0.0)	1 (4.2)	1 (4.2)
Reproductive system and breast disorders	1 (4.2)	1 (4.2)	0 (0.0)	2 (8.3)
Dysmenorrhea	1 (4.2)	1 (4.2)	0 (0.0)	2 (8.3)

The adverse experience will appear under the treatment when it first began.
Although a subject may have had two or more clinical adverse experiences, the subject is counted only once within a category by treatment. The same subject may appear in different categories.
FACT = Famotidine/Antacid Combination Tablet; EZ = Famotidine/Antacid EZ Chew tablet without water; EZw = Famotidine/Antacid EZ Chew tablet with water

Data Source: [16.4.2.1]

A total of 10 nonserious clinical adverse experiences were reported among the 7 subjects who reported an adverse experience. Of the 10 nonserious clinical adverse experiences reported, the most common clinical adverse experiences reported in the study was a headache (5). The investigator assessed flatulence and headache to be related to study drug. An episode of vasovagal syncope occurred in a non-treatment period.

No clinically meaningful lab abnormalities were noted in the study and no women were pregnant or became pregnant during the study.

Bioequivalence Conclusions
1. Famotidine/antacid combination EZ Chew tablet without water and famotidine/antacid combination tablet with water are bioequivalent with respect to AUC and C_{max}.
2. Famotidine/antacid combination EZ Chew tablet with water and famotidine/antacid combination tablet with water are bioequivalent with respect to AUC and C_{max}.
3. Famotidine/antacid combination EZ Chew tablet taken without water and with water and famotidine/antacid combination tablets taken with water were generally safe and well tolerated in this study.

See the biopharmacology review for further detail and comments on this study.

4 Efficacy Summary

No new clinical trail data for efficacy were submitted for this supplement.

5 Safety Summary

No new clinical trial or post-marketing safety data were submitted for this supplement. Substantial clinical and post-marketing experience exists with famotidine and with famotidine and antacid combination tablets, and no additional safety or efficacy clinical trials were deemed necessary in this development program. No serious adverse events were seen in bioequivalence Study 145, and no subject withdrew from the study due to an adverse experience. All adverse experiences resolved, and no new or unexpected adverse experiences were seen in this study. No new safety concerns are raised by this submission.

6 Pediatrics

Merck Consumer Pharmaceuticals Co. requests a waiver of pediatric studies for a newly formulated Nonprescription Famotidine Chewable Tablets (10 mg + Antacid), according to the final Pediatric Rule (21 CFR 314.55(a) and 601.27(a)).

Approved labeling for Pepcid™ Complete Tablets, an OTC product containing famotidine 10 mg plus antacid, allows for the treatment of individuals 12 years of age and older. The rationale for this age limit is that children below the age of 12 years should not use this product except under the direction of a physician, and a pediatric waiver was granted by FDA for the approved Pepcid Complete product.

The proposed labeling for the new formulation of Pepcid™ Complete will be very similar to the approved FDA labeling currently in the marketplace. There is no plan to label the reformulated 10 mg plus antacid product for use by children less than 12 years of age.

MO Comment: A full waiver for pediatric studies for Pepcid Complete was granted on March 22, 2001. This submission does not trigger PREA as this is not a new formulation (the RLD and the new product are both chewable tablets).

7 Labeling

The product label states Pepcid Complete has a "(b) (4)" on the principal display panel. See the IDS review for detailed label comments.

MO Comment: It is not clear what "(b) (4)" means since (b) (4) refers to a texture. The Sponsor needs to propose a different phrase and remove "(b) (4)" from the label.

8 Conclusion and Recommendation

The applicant has demonstrated that the new Famotidine/Antacid EZ Chewable Tablet is bioequivalent to the Famotidine/Antacid Combination Chewable Tablet. The product can be taken with or without water and the pharmacokinetic characteristics will not be significantly altered. No new safety concerns are raised in this submission. The acid neutralizing capacity is acceptable according to the chemist. The term "(b) (4)" on the principal display panel is not acceptable and will need to be deleted from the label. A pediatric waiver was previously granted by the FDA for the Pepcid Complete product in 2001, and PREA is not triggered as the new formulation is still a chewable tablet. It is recommended that this NDA be approved provided that no other issues arise in the chemistry and biopharmacology reviews.

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

/s/

Linda Hu
10/23/2008 05:33:57 PM
MEDICAL OFFICER

Daiva Shetty
10/24/2008 08:27:05 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW

1. ORGANIZATION CDER/ONDQA Division of Post-Marketing Evaluation HFD-560	**2. NDA #** 20-958 Original NDA approved:
3. NAME AND ADDRESS OF APPLICANT Merck & Co. Inc. Sumneytown Pike P.O. Box 4, BLA-33 West Point, PA 19486	**4. SUPPLEMENT** SCF-015 18-JUL-2008 (Rec. 18-JUL-2008)
	5. Name of the Drug Pepcid™ Complete Tablets
	6. Nonproprietary Name nonprescription famotidine, 10 mg Antacid Calcium Carbonate and Magnesium Hydroxide tablets
7. SUPPLEMENT PROVIDES for a modified product formulation, EZ Chews, of Pepcid™ Complete Chewable Tablets (famotidine 10 mg +Antacid).	**8. AMENDMENT** -- 18-JUL-08 BC; 08-AUG-08 SCF; 12-SEP-08 SCF; 19-SEP-08 SCF; 28-OCT-08 SCF; 29-OCT-08 SCF; 05-NOV-08 SCF

9. PHARMACOLOGICAL CATEGORY Prevention of heartburn and as an antacid	**10. HOW DISPENSED** OTC	**11. RELATED** DMF (b) (4)
12. DOSAGE FORM Tablets	**13. POTENCY** 10 mg famotidine, 800 mg calcium carbonate and165 mg magnesium hydroxide /tablet	

CHEMICAL NAME AND STRUCTURE See USAN

15. COMMENTS This application is submitted as a PA Supplement. The reformulated famotidine antacid combination tablet (FACT) will replace the current Pepcid™Complete tablet currently in the marketplace, and will retain the Pepcid™ Complete name. The proposed modified EZ Chew formulation provides for a softer chewable tablet with an improved taste and (b) (4). Only (b) (4) have been made to the proposed formulation. The flavors and other excipients are based on the currently approved 20mg famotidine chewable tablets described in NDA 20-801. The three flavors are berry, mint, and a new tropical fruit flavor. There are (b) (4) . All tests and limits for the proposed product are the same as for the currently marketed product, with the exception of description, famotidine assay methodology, the calculation for magnesium hydroxide assay, and the microbiological limits. The drug product specification for description has been updated to include the revised tablet color, shape and odor. The changes are evaluated in the CMC review. The stability data at the 6-month timepoints for all conditions supports the 36-month expiry date currently approved for Pepcid Complete Tablets.

16. CONCLUSIONS AND RECOMMENDATIONS Sufficient data is provided in the Supplement to demonstrate the quality of the reformulated famotidine antacid combination tablet (FACT). The Pepcid™ Complete tablet currently in the marketplace can be replaced, and the new EZ Chew tablet formulation can retain the Pepcid™ Complete name. From a CMC perspective, this Supplement can be Approved. OND will issue the Action Letter.

17. REVIEWER NAME (AND SIGNATURE) Sharon Kelly, PhD **filename:** 20-958#015 NDA	**DATE COMPLETED** 10-NOV-2008 **R/D INITIATED BY**

DISTRIBUTION: Original: NDA 20-958#015 cc: Division File CSO Reviewer

AP

Chemist's Introduction

Pepcid® Complete EZ Chews Tablets is a reformulation of the currently marketed Pepcid® Complete Chewable Tablets. The label claim of active ingredient levels of famotidine (10mg), calcium carbonate (800mg), and magnesium hydroxide (165mg) is the same for the current approved Pepcid® Complete formulations, (b) (4) (mint flavor) and (b) (4) (berry flavor), and for the proposed Pepcid® Complete EZ Chews Tablets products (b) (4) (berry flavor), (b) (4) (mint flavor), and (b) (4) (tropical fruit flavor). The products use the same (b) (4), which is sourced from the approved McNeil Consumer Healthcare, Las Piedras, PR manufacturing facility. The proposed Pepcid® Complete EZ Chews Tablets will be manufactured at the approved Johnson & Johnson Merck Consumer Pharmaceuticals Co.'s Lancaster manufacturing facility utilizing the same equipment and similar (b) (4) processes as the current Pepcid® Complete Chewable Tablets.

Chemistry Assessment

(b) (4)

35 Pages have been Withheld as b4 (CCI/TS) immediately following this page

---

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

/s/

Sharon Kelly
11/12/2008 03:05:44 PM
CHEMIST

Liang Zhou
11/12/2008 03:07:22 PM
CHEMIST
for BC, Dr. H Patel

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY REVIEW

NDA	20-958 S-015	*Submission Date(s)*	7/18/2008 8/8/2008 10/28/2008
Brand Name		Pepcid Complete	
Generic Name		Famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg	
Reviewer		Insook Kim, Ph.D.	
Team Leader		Sue-Chih Lee, Ph.D.	
OCP Division		Division of Clinical Pharmacology III	
OND Division		Division of Non-Prescription Products	
Sponsor		Merck & Co. Inc.	
Relevant IND		50,534	
Submission Type; Code		SCF	CMC supplement
Formulation; Strengths; Regimen		• Chewable tablet, • Famotidine 10 mg, Calcium carbonate 800 mg; Magnesium hydroxide 165 mg • Directions Adults and children 12 years and over: • Do not swallow tablet whole: chew completely • To relieve symptoms, chew 1 tablet before swallowing • Do not use more than 2 chewable tablets in 24 hours Children under 12 years: ask a doctor	
Indication		Relieve heartburn associated with acid indigestion and sour stomach	

Table of Contents

1 Executive Summary 2
1.1 Recommendations 2
1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings 2
2 Question-Based Review 3
2.1 General Attributes of the drug 4
2.5 General Biopharmaceutics 4
2.6 Analytical Section 6
4 Appendices 8
4.1. Proposed labeling 8
4.2. Individual Study Review 9

1 Executive Summary

1.1 Recommendations

The division of Clinical Pharmacology 3 reviewed the submitted application including a bioequivalence study report and found it acceptable from a clinical pharmacology standpoint.

Of note, comparison of the Acid Neutralizing Capacity between the to-be-marketed product and the reference product was requested by the Agency and the study result is being reviewed by CMC reviewer.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

In this Prior Approval Supplement, the sponsor provides for changes in the Labeling, Chemistry, Manufacturing and Controls, and the final study report of an in vivo BE study in support of a new formulation (EZ Chews; To-be-marketed formulation; TBM) of the approved PEPCID^{TM} Complete chewable tablet. The sponsor stated that the new formulation will replace the current PEPCID^{TM} Complete tablet. In a teleconference with the sponsor held on October 24, 2007, the Agency recommended that an in vivo bioequivalence study be conducted as the proposed formulation change is considered a Level 3 change per SUPAC-IR. In addition to a bioequivalence study, the Agency advised the sponsor that Acid Neutralization Capacity (ANC) equivalence data would be required. For a review of ANC results, please see CMC review by Sharon Kelly.

Bioequivalence

Bioequivalence between the TBM chewed without water or with water and PEPCID^{TM} Complete chewable tablet with water was evaluated in a study (P145) titled :A single-dose, open-label, three-period crossover study to assess the bioequivalence of Famotidine/Antacid Combination Tablets (FACT) compared to Famotidine/Antacid EZ Chew tablet without water and Famotidine/Antacid EZ Chew Tablet with water". The bioequivalence was assessed based on the ratios of Cmax and $AUC_{(0\text{-inf})}$ after administration of FACT chewed with 120 mL water and after TBM chewed with 120 mL water or without water. A total of 24 male and female subjects were enrolled and completed the 3 period crossover study and study results from all 24 subjects were used for BE assessment.

The bioequivalence between FACT administered by chewing with water and EZ Chew administered by chewing without water was demonstrated by the 90% confidence interval for the geometric mean ratios (EZ/FACT) for AUC (0-inf) and Cmax falling within the BE criteria of (0.80, 1.25). (Table 1.) The $AUC_{(0\text{-inf})}$ and Cmax geometric mean ratios for FACT with water and EZ Chew without water were 1.05 and 1.03, respectively and the 90% confidence interval were (0.98, 1.13) and (0.93, 1.13). The median apparent half-life was 4.60 and 4.56 hours, respectively and the median Tmax was 1.25 and 1.75 hours.

The bioequivalence between FACT administered by chewing with water and EZ Chew administered by chewing with water was demonstrated by the 90% confidence interval for the geometric mean ratios (EZ/FACT) for $AUC_{(0\text{-inf})}$ and Cmax fall within the BE criteria of (0.80, 1.25) (Table 1.) The AUCinf and Cmax geometric mean ratios for FACT and EZ chew with water were 1.05 and 1.03, respectively and the 90% confidence interval were (0.98, 1.13) and (0.93, 1.14). The median apparent half-life was 4.60 and 4.16 hours, respectively and the median Tmax was 1.25 and 1.50 hours.

Table 1

Pharmacokinetic Parameters of $AUC_{0-\infty}$ and C_{max}
Summary of FACT Versus EZ Chew With and Without Water (N=24)

Pharmacokinetic Parameter	N	Geometric Mean			Geometric Mean Ratio		MSE
		(FACT) with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)	
$AUC_{0-\infty}$ (ng/mL hr)	24	248.0 (216.4, 284.2)	261.2 (227.9, 299.3)	260.1 (227.0, 298.0)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	0.022
C_{max} (ng/mL)	24	44.4 (38.1, 51.7)	45.5 (39.1, 52.9)	45.9 (39.4, 53.4)	1.03 (0.93, 1.13)	1.03 (0.93, 1.14)	0.044

Geometric Means based on least square estimates from an ANOVA performed on natural log-transformed values
MSE=Mean Square Error on log scale
Test for Carryover Effect was non-significant: AUC p-value= 0.965, Cmax p-value= 0.980

Data Source: [16.4.4.1; 16.4.4.2]

Reviewer's comment: The bioequivalence between the reference product (FACT) and TBM (EZ Chew) with water and without water was adequately established. Therefore, **t**he to-be-marketed product can be taken with or without water after chewed completely. Since bioequivalence between TBM swallowed whole and taken after complete chewing was not established, TBM should not be swallowed whole. The proposed Trade Carton Label (see section 4.1.) states it accordingly.

Acid Neutralization Capacity (ANC)

The sponsor stated that ANC test methods and specification is the same as the currently marketed Pepcid™ Complete test method. Acid Neutralization Capacity testing was conducted using the current ANC test method for formulas (b) (4) (current Mint), (b) (4) (current Berry), (b) (4) (proposed Berry), (b) (4) (proposed Mint), and (b) (4) (Tropical Fruit). All results are within the ANC product specification of (b) (4) mEq per tablet. Please, see a CMC review by Dr. Sharon Kelly for detail.

2 Question-Based Review

2.1 General Attributes of the drug

2.1.1 What pertinent regulatory background contributes to the current assessment of the bioequivalence study of this drug?

Reviewer's comment: *The new formulation will be referred as To-Be-Marketed formulation (TBM). The To-Be-Marketed formulation is also referred to as EZ Chew formulation in the study report. The reference PEPECID Complete chewable tablet currently on the market is also referred to as "FACT".*

Famotidine is a potent, competitive, and reversible inhibitor of histamine action at the H2 receptor. Nonprescription famotidine FCT (film-coated tablet) was approved in the United Sates in 1995 at the 10 mg strength and in 2003 at the 20 mg strength for the relieve of heartburn associated with acid indigestion and sour stomach, and for the prevention of these symptoms brought on by consuming food and beverages that are known to cause these symptoms. It is also approved in the U.S. as a prescription agent for the short-term treatment of active duodenal ulcer and active benign gastric ulcer, maintenance therapy of duodenal ulcer disease at doses up to 20 mg BID. It is labeled for treatment of pathological hypersecretory conditions such as, Zollinger-Ellison syndrome at doses up to 640 mg/day.

PEPCID™ Complete, a (b) (4) chewable tablet (CCT) containing famotidine 10 mg, $CaCO_3$ 800 mg, and Mg $(OH)_2$ 165 mg is currently approved in the United States for relief of heartburn associated with acid indigestion and sour stomach. The antacid component of this tablet provided 21 mEq of acid neutralizing capacity (ANC).

The sponsor has developed a new chewable formulation (To-be-marketed formulation: also referred as EZ Chew formulation in the study report) of famotidine + antacid to (b) (4) (b) (4) when the product is chewed. The amount of active ingredient in the new formulation will not change from the currently approved product (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg)(Table 2).

In this Prior Approval Supplement, the sponsor provides for changes in the Labeling, Chemistry, Manufacturing and Controls, and the final study report of an in vivo BE study in support of a new formulation (EZ Chews; To-be-marketed formulation; TBM) of the approved PEPCID™ Complete tablet. The sponsor stated that the new formulation will replace the current PEPCID™ Complete tablet. In a teleconference with the sponsor held on October 24, 2007, the Agency recommended that an in vivo bioequivalence study be conducted as the proposed formulation change is considered a Level 3 change per SUPAC-IR and the Agency also advised the sponsor that Acid Neutral Capacity (ANC) equivalence data would be required.

2.5 General Biopharmaceutics

2.5.1 Is the proposed to-be-marketed formulation bioequivalent to the reference product?

Study P145 was conducted to evaluate the bioequivalence between the to-be-marketed formulation (TBM; EZ Chew) and the reference product FACT. The TBM is bioequivalent to the reference product FACT regardless of concomitant water intake.

Study P145 was a single-dose, open-label, and three-period crossover study to assess the bioequivalence of famotidine/antacid combination tablets (FACT, current PEPCID™ Complete tablet on market) compared to famotidine/antacid EZ chew tablet without water and famotidine/antacid EZ chew tablet with water. There was a 5-7-day washout period between each treatment period. The duration of the entire study was approximately 6 weeks.

Table 2. Comparison of composition and component of TBM and the reference product

Tablet Formula Comparison

INGREDIENT	Function	Quality Reference	REFERENCE PRODUCT THAT IS CURRENTLY ON THE MARKET Mint (b) (4) Weight, mg (percentage of total tablet)	TEST PRODUCT Mint (b) (4) Weight, mg (percentage of total tablet)	Test Product Changes from Reference Product.
(b) (4)	Active	Manufacturer's Specification	(b) (4)	(b) (4)	None, same formula and process in reference and test product. Delivers 10mg of Famotidine to support label claim.
Calcium Carbonate / (b) (4) (b) (4) (b) (4)	Active	Manufacturer's Specification	APPEARS THIS WAY ON ORIGINAL	(b) (4)	(b) (4)
Magnesium Hydroxide USP ((b) (b) (4)	Active	Manufacturer's Specification	(b) (4)	APPEARS THIS WAY ON ORIGINAL	
(b) (4)	Active	Manufacturer's Specification	(b) (4)		
(b) (4)	(b) (4)	Manufacturer's Specification	(b) (4)		Removed and replaced
(b) (4)	Flavor	Manufacturer's Specification	(b) (4)		
(b) (4)	Flavor	Manufacturer's Specification	(b) (4)		
(b) (4)	(b) (4)	Manufacturer's Specification	(b) (4)		
Dextrose Excipient NF (b) (4)	(b) (4)	NF	APPEARS THIS WAY ON ORIGINAL	(b) (4)	(b) (4)
(b) (4)	(b) (4)	NF	(b) (4)	APPEARS THIS WAY ON ORIGINAL	(b) (4)
Magnesium Stearate	(b) (4)	NF	(b) (4)	(b) (4)	(b) (4)
Sucralose NF (b) (4)	(b) (4)r	NF	APPEARS THIS WAY ON ORIGINAL	(b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	Manufacturer's Specification	APPEARS THIS WAY ON ORIGINAL	(b) (4)	(b) (4)
Crospovidone NF ((b) (4) (b) (4)	(b) (4)	NF		(b) (4)	(b) (4)
(b) (4)	Flavor	Manufacturer's Specification		(b) (4)	(b) (4)
FD&C Blue #1 Aluminum Lake	(b) (4) (b) (4)	Manufacturer's Specification		(b) (4)	(b) (4)
D&C Yellow #10 Aluminum Lake		Manufacturer's Specification		(b) (4)	
Total Weight	APPEARS THIS WAY ON ORIGINAL		(b) (4)	(b) (4)	(b) (4)

(b) (4)

(b) (4)

The bioequivalence between FACT administered with water and EZ Chew administered without water was demonstrated by the 90% confidence interval for the geometric mean ratios (EZ/FACT) for $AUC_{(0\text{-inf})}$ and Cmax falling within the BE criteria of (0.80, 1.25). The AUCinf and Cmax geometric mean ratios for FACT and EZ chew without water were 1.05 and 1.03, respectively and the 90% confidence interval were (0.98, 1.13) and (0.93, 1.13). The median apparent half-life was 4.60 and 4.56 hours, respectively and the median Tmax was 1.25 and 1.75 hours (Table 3).

The bioequivalence between FACT administered with water and EZ Chew administered with water was demonstrated by the 90% confidence interval for the geometric mean ratios (EZ/FACT) for $AUC_{(0\text{-inf})}$ and Cmax fall within the BE criteria of (0.80, 1.25). (Table 3). The AUCinf and Cmax geometric mean ratios for FACT and EZ chew with water were 1.05 and 1.03, respectively and the 90% confidence interval were (0.98, 1.13) and (0.93, 1.14). The median apparent half-life was 4.60 and 4.16 hours, respectively and the median Tmax was 1.25 and 1.50 hours.

Table 3.

Pharmacokinetic Parameters of $AUC_{0-\infty}$ and C_{max}
Summary of FACT Versus EZ Chew With and Without Water (N=24)

Pharmacokinetic Parameter	N	Geometric Mean			Geometric Mean Ratio		MSE
		(FACT) with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)	
$AUC_{0-\infty}$ (ng/mL hr)	24	248.0 (216.4, 284.2)	261.2 (227.9, 299.3)	260.1 (227.0, 298.0)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	0.022
C_{max} (ng/mL)	24	44.4 (38.1, 51.7)	45.5 (39.1, 52.9)	45.9 (39.4, 53.4)	1.03 (0.93, 1.13)	1.03 (0.93, 1.14)	0.044

Geometric Means based on least square estimates from an ANOVA performed on natural log-transformed values
MSE=Mean Square Error on log scale
Test for Carryover Effect was non-significant: AUC p-value= 0.965, Cmax p-value= 0.980

Data Source: [16.4.4.1; 16.4.4.2]

Pharmacokinetic Parameter	N	Treatment Statistics			Median Treatment Differences	
		FACT with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)
T_{max} (hr)	24	1.25	1.75	1.50	0.50 (0.00, 0.75)	0.50 (0.00, 0.75)
Apparent Half-Life (hr)	24	4.60	4.56	4.16	-0.26 (-0.70, 0.32)	-0.58 (-1.12, -0.04)

Harmonic means are report for Half-Life treatment statistics. Medians are report for Tmax treatment statistics.
Median treatment differences and confidence intervals are based on Hodges-Lehmann estimates.

Data Source: [16.4.4.1; 16.4.4.2]

2.6 Analytical Section

2.6.1 How are the active moieties identified and measured in the plasma/urine in the clinical pharmacology and biopharmaceutics studies?

In this application, submitted were the final reports of bioanalytical assay validation titled "Validation of a high performance liquid chromatographic method using tandem mass spectrometry detection and automated extraction for the determination of Famotidine in human EDTA K3 plasma" (b) (4) Study No. 82042RFY) and of bioanalytical study titled "Determination of Famotidine in human EDTA plasma in Merck & Co protocol MK-0208C PN145-00".

Briefly, the analyte Famotidine and its internal standard (b) (4) were extracted from a 0.100 mL aliquot of human EDTA plasma using an automated solid phase extraction procedure (Liquid Handling Systems) according to method SOP (b) (4). The extracted samples were injected into a liquid chromatograph equipped with an (b) (4) column. Two mobile phases were used. The mobile phase A was a mixture of water, methanol and formic acid (90/10/1) and the mobile phase B was a mixture of water, methanol and formic acid (25/75/1) and ammonium formate (b) (4) mM. The detection method used was tandem mass spectrometry.

2.6.3 What is the range of the standard curve? What are the lower and upper limits of quantification (LLOQ/ULOQ)? What is the accuracy and precision?

The validated calibration range for Famotidine in this assay is from 0.50 to 201.70 ng/mL. The LLOQ of Famotidine quantification was 0.50 ng/mL. The plasma concentrations of Famotidine were close to the LLOQ at 24 hour post-dose. The bioanalytical assay method was adequately validated with acceptable accuracy, precision and selectivity.

Table 4. In-run Intraday and Interday variability of the Famotidine plasma assay

QC sample	Concentration (ng/ml)	QC1 1.52	QC4 20.28	QC2 60.84	QC3 141.96
Intra day	Precision[1] (%)	3.64	2.81	3.2	2.76
	Accuracy[2] (%)	108.55	108.78	107.73	104.19
Interday	Precision[1] (%)	3.92	4.15	3.19	3.79
	Accuracy[2](%)	102.38	103.32	101.50	100.20

1: Coefficient of variation
2: Expressed as [(mean observed concentration)/ (nominal concentration)] x 100

1 Page of Draft Labeling has been removed as b4 (CCI/TS) immediately following this page

4.2. Individual Study Review

Reviewer's note: The reference product, PEPCIDTM COMPLETE tablet is referred as Famotidine/antacid combination tablets (FACT) whereas the to-be-marketed formulation is referred as FAMOTIDINE/antacid EZ chew tablet (EZ Chew) in the study report.

Study P145
A single-dose, open-label, three-period crossover study to assess the bioequivalence of Famotidine/antacid combination tablets (FACT) compared to Famotidine/antacid EZ chew tablet without water and Famotidine/antacid EZ chew tablet with water

Study design
Open-label, single dose, randomized, 3-period crossover study in 24 healthy subjects to assess the bioequivalence of famotidine/antacid EZ Chew tablet taken without water and with water compared to FACT (PEPCID Complete tablet, U.S. marketed formulation) taken with water. Following a single dose of each treatment, subjects will be confined to the study unit for at least 24 hours for plasma collection. Each treatment period will be separated by 5 to 7 days, with a total duration of approximately 6 weeks.

Subject disposition
Twenty-four healthy male and female subjects aged 18 to 45 years were enrolled and completed all three periods.

Dosage/dosage form, route, and dose regimen
Treatments were administered in the morning after an overnight fast, on the respective treatment days between 6 AM and 9 AM. The order in which subjects receive treatments was determined by a random allocation schedule.

- Treatment A: a single-dose of FACT with 120 mL of water
- Treatment B : a single-dose of famotidine/antacid combination EZ Chew tablet without water
- Treatment C: famotidine/antacid combination EZ Chew tablet with 120 mL of water.

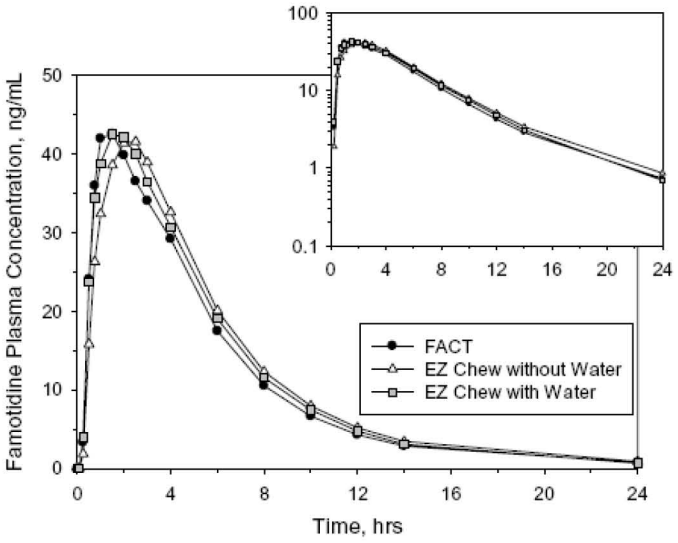
Results

Following a single dose administration of FACT or EZ Chew tablet, the peak plasma concentrations were achieved about 1-2 hours post-dose. The mean peak plasma concentrations were about 45 ng/mL and the mean AUCinf was 240-260 ng/mL hr (Figure 4.2.1.; Table 4.2.1.)

The plasma concentrations at 24 hours post-dose were close to LLOQ and the (% AUCext) was <5% for all assessments.

Figure 4.2.1.

Arithmetic Mean Famotidine Plasma Concentration Profiles
Following Administration of Single Doses of
FACT with Water, EZ Chew without Water, and EZ Chew with Water
to Healthy Male and Female Subjects
(N=24/Treatment; Inset = Semilog Scale)



The EZ Chew tablet was bioequivalent with or without water to FACT tablet (Table 4.2.1.) supported by a 90% confidence interval for ratios of Cmax and AUC falling within the pre-specified bioequivalence criteria (0.80-1.25).

Table 4.2.1.

Pharmacokinetic Parameters of $AUC_{0-\infty}$ and C_{max}
Summary of FACT Versus EZ Chew With and Without Water (N=24)

Pharmacokinetic Parameter	N	Geometric Mean			Geometric Mean Ratio		MSE
		(FACT) with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)	
$AUC_{0-\infty}$ (ng/mL hr)	24	248.0 (216.4, 284.2)	261.2 (227.9, 299.3)	260.1 (227.0, 298.0)	1.05 (0.98, 1.13)	1.05 (0.98, 1.13)	0.022
C_{max} (ng/mL)	24	44.4 (38.1, 51.7)	45.5 (39.1, 52.9)	45.9 (39.4, 53.4)	1.03 (0.93, 1.13)	1.03 (0.93, 1.14)	0.044

Geometric Means based on least square estimates from an ANOVA performed on natural log-transformed values
MSE=Mean Square Error on log scale
Test for Carryover Effect was non-significant: AUC p-value= 0.965, Cmax p-value= 0.980

Data Source: [16.4.4.1; 16.4.4.2]

Pharmacokinetic Parameter	N	Treatment Statistics			Median Treatment Differences	
		FACT with Water (95% CI)	EZ Chew without Water (95% CI)	EZ Chew with Water (95% CI)	EZ Chew without Water / FACT (90% CI)	EZ Chew with Water / FACT (90% CI)
T_{max} (hr)	24	1.25	1.75	1.50	0.50 (0.00, 0.75)	0.50 (0.00, 0.75)
Apparent Half-Life (hr)	24	4.60	4.56	4.16	-0.26 (-0.70, 0.32)	-0.58 (-1.12, -0.04)
Harmonic means are report for Half-Life treatment statistics. Medians are report for Tmax treatment statistics. Median treatment differences and confidence intervals are based on Hodges-Lehmann estimates.						

Data Source: [16.4.4.1; 16.4.4.2]

Figure 4.2.2. Individual AUC and Cmax Ratios of (EZ without Water/FACT with Water)

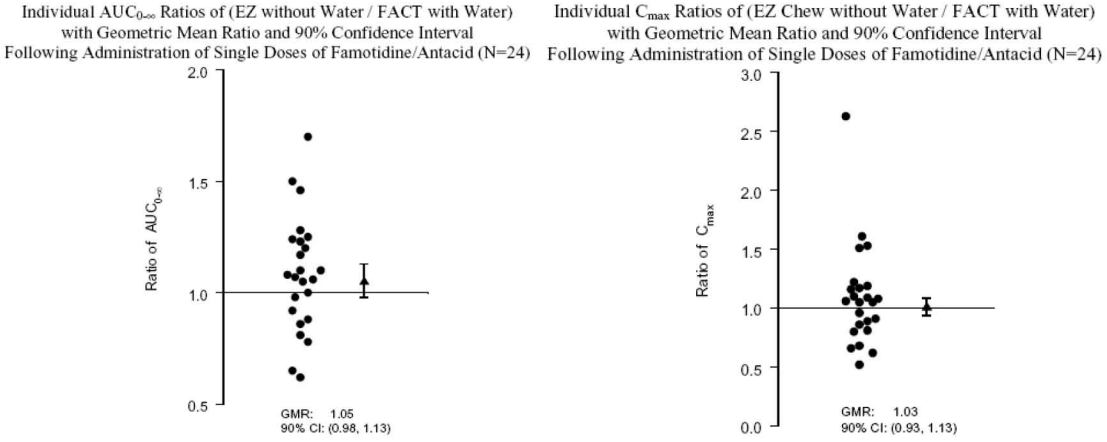
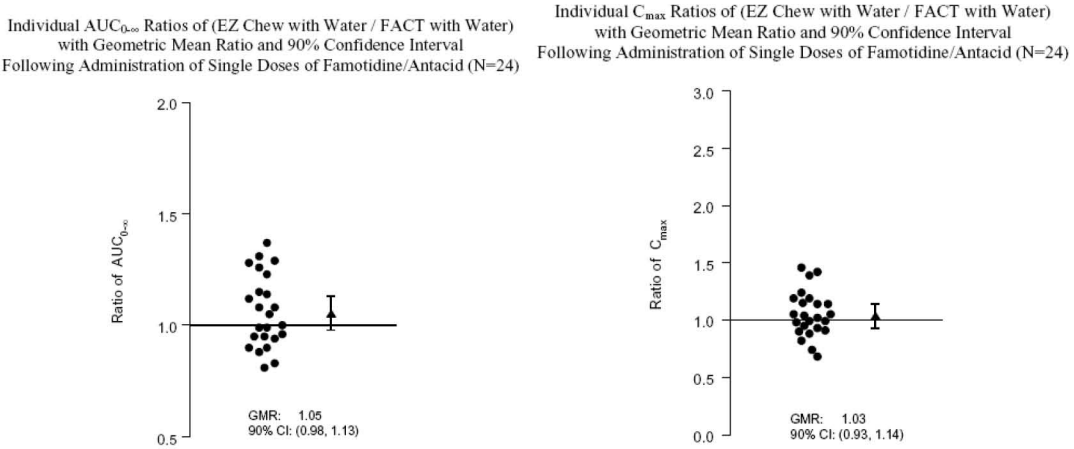


Figure 4.2.3.Individual AUC and Cmax Ratios of (EZ with Water/FACT with Water)



Reviewer's comment: The individual AUC ratios of EZ Chew without water/FACT with water were more variable ranging from 0.62 to 1.70 (Figure 4.2.2.) than the ratios of EZ Chew with water/FACT with water which ranged from 0.81 to 1.37(Figure 4.2.3.).

Similarly, the individual Cmax ratios of EZ Chew without water/FACT with water ranged from 0.52 to 2.63 while Cmax ratios of EZ Chew with water/FACT with water were from 0.68 to 1.46.

Sponsor's Conclusion

The to-be-marketed formulation, Famotidine/antacid combination EZ Chew tablet without water and PEPCIDTM Complete tablet with water are bioequivalent with respect to AUCinf and Cmax.

The to-be-marketed formulation, Famotidine/antacid combination EZ Chew tablet with water and PEPCIDTM Complete tablet with water are bioequivalent with respect to AUCinf and Cmax.

Reviewer's comments: The study design is adequate and the sponsor's conclusion is acceptable. Therefore, the to-be-marketed product can be taken with or without water after chewed completely. Since bioequivalence after intake of chewed tablet and whole tablet was not established, the to-be-marketed product should not be taken as a whole tablet. The proposed package insert states it accordingly.

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

/s/

Insook Kim
11/5/2008 02:16:28 PM
BIOPHARMACEUTICS

Sue Chih Lee
11/5/2008 02:18:14 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

OTHER REVIEW(S)

Labeling Supplement Review

SUBMISSION DATE:	July 18, 2008, October 29, 2008
NDA/REPORT#	NDA 20-958/SCF-015 and BL
Drug Product	PEPCID Complete Tablets
Sponsor/Contact	Paulette Midgette, MS Manager, Regulatory Affairs Worldwide OTC Regulatory Affairs Johnson & Johnson – Merck Consumer Pharmaceuticals Co.
Active Ingredients	Famotidine (10mg) Calcium carbonate (800mg) Magnesium hydroxide (165mg)
Labeling	5-ct carton (Tropical Fruit) 8-ct carton (b) (4) Tropical Fruit) 25 x 1-ct dispensit carton (Tropical Fruit) 25-ct bottle (Berry, Cool Mint, Tropical Fruit) 50-ct bottle (Berry, Cool Mint, Tropical Fruit) 100-ct bottle (Berry) 1-ct Sample Pouch (Berry, Cool Mint, Tropical Fruit) 1-ct Trade Pouch (Mint, Tropical Fruit)
Reviewer	Mary S. Robinson
Review Date	October 13, 2008

Background

This submission was submitted by Johnson and Johnson - Merck and Company, Inc. on July 18, 2008\to provide for a change s in labeling for Pepcid Complete in support of a new product formulation. The newly formulated product will replace the Pepcid Complete product currently in the marketplace. The proposed trade name, "Pepcid Complete" for the new formulated product is identical to that of the FDA approved brand name for the famotidine 10 mg + antacid chewable tablet product (Pepcid Complete, NDA 20-958, approved October 16, 2000).

Modifications to the currently approved Pepcid Complete chewable tablets formulation are made to allow for a (b) (4) tablet. The amount of active ingredients in the new chewable formulation is not changed from the currently approved product (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg). There are only (b) (4) in the new formulation to (b) (4) (See CMC review for (b) (4)).

The sponsor states that the proposed product label for the EZ Chews formulated Pepcid Complete chewable tablets is identical to the last approved labeling (NDA 20958/SLR-013) and the current product label in the marketplace, with the following exceptions:

1. The text and artwork on the Principal Display Panel are consistent with currently approved packaging for the entire Pepcid OTC product line with the exception of a flag containing the phrase (b) (4)" or "New Flavor" (addition of new tropical fruit flavor).
2. Three Flavors of the new product will be offered, Berry, Cool Mint, and Tropical Fruit, and each flavor has minor variations to (b) (4) ingredients listed in (b) (4) (See CMC Review for (b) (4)).

3. Modifications to (b) (4) listed in (b) (4) ingredients section of Drug Facts have been made for the new tablet formulation.

4. The tablet image has been changed to display the new tablet image for the EZ Chews formulated product.

On October 29, 2008, the sponsor submitted new labeling. This submission was in response to FDA correspondence dated October 21, 2008 that stated that the banner statement (b) (4)," on the PDP of the Cool Mint and Berry flavored variants was not acceptable. The sponsor states that the revisions for the Mint and Berry flavored products were made to the PDP only. The text and artwork on the PDP are consistent with the July 18, 2008 submission, with the exception that the banner is changed on the Berry and Cool Mint flavor Pepcid Complete cartons and containers from " (b) (4)" to read: "New Taste." Also all labeling for SKUs that are to be marketed have been included in this amendment, including the addition of two label units, Berry 1-count sample pouch and Mint 1-count sample pouch.

This amendment withdraws the (b) (4) Carton. The sponsor stated that in accordance with FDA guidelines "New Taste" and "New Flavor" will be removed from product labeling 6 months after introduction into the marketplace.

This submission updates the Pepcid Complete Chewable Tablets labeling. The sponsor states that no other changes were made to the labeling approved October 16, 2000.

This submission contains draft color artwork printed labeling for the Pepcid Complete Chewable tablets cartons and containers.

This is a review of the labeling contained in July 28, 2008 and October 29, 2008 submissions for NDA 20-958/SLR-015.

Reviewer's comments

I. Cartons and bottle labels

A. Principal Display Panel: (5-ct and 8-ct cartons (Tropical Fruit), 25 X 1 dispensit carton (Tropical Fruit), 25-ct bottle (Berry, Cool Mint, Tropical Fruit), 50-ct bottle (Berry, Cool Mint, Tropical Fruit), 100-ct bottle (Berry))

The text and artwork on the Principal Display Panels are consistent with currently approved packaging for the entire Pepcid OTC product line with the exception of the following:

1. A flag containing the phrase "NEW Taste" is added above the words "Dual Action" on the Cool Mint, and Berry flavors. This replaces the flag containing the statement (b) (4) from the July 18, 2008 submission.

This is acceptable. The flags on the Cool Mint Flavor and the Berry Flavor are to be deleted from the PDP after 6 months following market introduction

2. The text and artwork on the PDP for the new tropical fruit flavor is consistent with the Berry and Cool Mint flavors, except for the flavor description and fruit graphic denoting the tropical fruit flavor. The fruit graphic for the new Tropical fruit flavor is denoted by pill on banana and pineapple. The flag above the words "Dual Action" for this flavor read: "New Flavor".

This is acceptable. The flag on the Tropical Fruit flavor is to be deleted from the PDP after 6 months following market introduction.

3. Lower left corner, the pill images for the flavors are changed to appear more 3 dimensional. The Cool Mint, Berry, and Tropical Fruit pill colors are white, pink and yellow, respectively.

This is acceptable.

B. Drug Facts ((5-ct and 8-ct cartons (Tropical Fruit), 25 X 1 dispensit carton (Tropical Fruit), 25-ct bottle (Berry, Cool Mint, Tropical Fruit), 50-ct bottle (Berry, Cool Mint, Tropical Fruit), 100-ct bottle (Berry))

1. The "Drug Facts" text for the new Tropical Fruit flavor is the same as that approved for the Berry and Cool Mint flavors except under the inactive ingredients section. The inactive ingredients differ between the three flavors because of minor variations (b) (4) ingredients.

This is acceptable.

2. Under "Other information", bullet one, "calcium (b) (4) mg; magnesium (b) (4) mg" is changed to "calcium 320 mg; magnesium 70 mg".

This is acceptable under §§ 201.70 and71.

5-ct carton,

3. The Tips for managing heartburn, the Flexible Spending Account symbol information, store brand statement "The makers of Pepcid Complete do not manufacture store brands" and the distribution statement are moved from the side panel to the back panel.

This is acceptable.

4. The "Drug Facts" 2 column format is changed to a 1 column format.

This is acceptable.

8-ct carton

5. The "store brand statement" is repeated above the "Drug Facts".

This is acceptable. However under 21 CFR 211.132 (c)(ii) the tamper-evident statement needs to be prominently placed on the package. Thus, it needs to be at least as prominent as the store brand statement. The sponsor should be asked to increase the prominence of the tamper-evident statement.

25 X 1 Dispensit Carton

6. The labeling for the 25 x 1 dispensit carton is acceptable.

7. Side panel. The Flexible spending account information, graphics and Pepcid commitment statement is added.

This is acceptable.

8. Back panel. Above the "Drug Facts', the graphics are modified to be consistent with the previously approved labeling in NDA 20958/SLR-013.

This is acceptable.

II. Bottle Containers (25-ct bottle (Berry, Cool Mint, Tropical Fruit), 50-ct bottle (Berry, Cool Mint, Tropical Fruit), 100-ct bottle (Berry))

Other Labeling (labeling following "Drugs Facts")
1. Following "Tips for Managing Heartburn" the image of a pill is added and is color-coded to represent the fruit flavor of the pill.

This is acceptable.

2. On the 25- and 50-count containers, the store brand statement "The makers of Pepcid Complete do not manufacture store brands" is added to the lower portion of the side panel below the first portion of the "Drug Facts" information. The Pepcid promotional mail-in offer is deleted from the labeling.

This is acceptable. However, this layout is not compliant with 21 CFR 201.66(d)(7) that requires that there be no graphical images or text not described in § 201.66(c) to interrupt the required title, headings and subheadings. However, this portion of the regulation is open to interpretation, and this layout has been approved in previous supplements.

III. Pouch
1. The Berry, Tropical Fruit, Cool Mint sample pouches are acceptable.

This is acceptable.

2. The Cool Mint and Tropical Fruit trade pouches are acceptable.

Reviewer's Recommendations

1. Inform the sponsor that the draft labeling for the 5-ct and 8-ct cartons (Tropical Fruit), 25 X 1 dispensit carton (Tropical Fruit), 25-ct bottle (Berry, Cool Mint, Tropical Fruit), 50-ct bottle (Berry, Cool Mint, Tropical Fruit), and 100-ct bottle (Berry) is acceptable, including the following changes:
   a. The inactive ingredients changes relating to excipients in the new formulation.
   b. A flag containing the phrase "New Taste" for the Berry and Cool Mint flavors.
   c. A flag containing the phrase "New Flavor "for the Tropical Fruit flavor.
   d. Changes in the pill images to appear more three dimensional on the Berry and Cool Mint flavors.
   e. The rounding of the reported amounts of calcium, and magnesium in the product to the nearest 5 mg per 21 CFR 211.70 and 71.

2. The annotated font specifications in these submissions are acceptable.

3. The sponsor should be asked to increase the prominence of the Tamper-evident statement on the cartons and containers. If the sponsor chooses to increase the font only, then this change can be submitted with the final printed labeling.

3. Remind the sponsor to remove "New Taste" and "New Flavor" on the principal display of the cartons and containers 6 months after introduction in the market place.

38 pages of Drafat Labeling have been Withheld as b4 (CCI/TS) immediately following this page

---

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

/s/

Mary Robinson
11/10/2008 04:40:06 PM
INTERDISCIPLINARY

Debbie Lumpkins
11/10/2008 04:42:11 PM
INTERDISCIPLINARY

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-958/S015

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 20-958/S-015 **PRIOR APPROVAL SUPPLEMENT**

Merck & Co., Inc.
Attention: Paulette Midgette
Manager, Regulatory Affairs
Worldwide OTC Regulatory Affairs
Sumneytown Pike, P.O. Box 4, UN-D129
West Point, PA 19486

Dear Ms. Midgette:

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

Name of Drug Product:	Pepcid Complete (10 mg famotidine, 800 mg calcium carbonate and 165 mg magnesium hydroxide) chewable tablets
NDA Number:	20-958
Supplement number:	015
Date of supplement:	July 18, 2008
Date of receipt:	July 18, 2008

This supplemental application proposes the following changes: the replacement of the current Pepcid™ Complete product with a new chewable tablet formulation, with associated revisions to the labeling, CMC and Pharmacology & Bioavailability/Bioequivalence sections of the NDA.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on September 16, 2008 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be November 18, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Nonprescription Products
Division of Nonprescription Clinical Evaluation
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have questions, call Mary Vienna, Regulatory Project Manager, at (301) 796-4150.

Sincerely,

{See appended electronic signature page}

Leah Christl, Ph.D.
Acting Chief, Project Management Staff
Division of Nonprescription Clinical Evaluation
Office of Nonprescription Products
Center for Drug Evaluation and Research

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

/s/

Leah Christl

7/28/2008 01:27:32 PM