PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

# PEPCID® COMPLETE®

Famotidine / Calcium Carbonate / Magnesium Hydroxide Chewable Tablets

10 mg Famotidine / 800 mg Calcium Carbonate / 165 mg Magnesium Hydroxide

Combination Histamine $H_2$-Receptor Antagonist and Antacid

McNeil Consumer Healthcare

Division of Johnson & Johnson Inc.

88 McNabb Street

Markham, Ontario

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## RECENT MAJOR LABEL CHANGES

| | |
|---|---|
| Section 9: Drug Interactions, Section 9.4: Drug-Drug Interactions | [02/2024] |

## TABLE OF CONTENTS

**Sections or subsections that are not applicable at the time of authorization are not listed.**

## PART I: HEALTH PROFESSIONAL INFORMATION

## 1 INDICATIONS

PEPCID® COMPLETE® (famotidine, calcium carbonate, magnesium hydroxide) is indicated for:

- the treatment of the following conditions where neutralization of gastric acid and a controlled reduction of gastric secretion is required, such as acid indigestion, heartburn, sour or upset stomach;
- the prevention of these symptoms when associated with the consumption of food and/or beverage

PEPCID® COMPLETE® relieves and prevents daytime heartburn symptoms and relieves heartburn during the night.

### 1.1 Pediatrics

**Pediatrics (<12 years of age):**
Safety and effectiveness in children have not been established. PEPCID® COMPLETE® should not be administered to children under 12 years of age.

### 1.2 Geriatrics

No dosage adjustment is required based on age (see 10.3 Pharmacokinetics).

## 2 CONTRAINDICATIONS

- Famotidine/Calcium Carbonate/Magnesium Hydroxide is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- Cross-sensitivity has been observed between $H_2$-receptor antagonists. Therefore, PEPCID® COMPLETE® should not be taken by individuals with a history of hypersensitivity to other drugs in this class of compounds.

## 4 DOSAGE AND ADMINISTRATION

### 4.1 Dosing Considerations

- If symptoms get worse or persist for more than two consecutive weeks, or if new symptoms develop, patients should be advised to stop use and consult a physician.
- Individuals with kidney disease should not take this product except on the advice of a physician. A dosage adjustment may be necessary in patients with moderate or severe renal impairment (creatinine clearance less than 60 mL/min/1.48 $m^2$). See 7 WARNINGS AND PRECAUTIONS.

- This product should not be taken within two hours of another medicine because the effectiveness of the other medicine may be altered.

### 4.2 Recommended Dose and Dosage Adjustment

For heartburn or acid indigestion (Adults and children 12 years and older):
For fast, long lasting and effective relief of symptoms: one (1) tablet (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg). If symptoms return, another tablet may be taken.

For prevention of acid-related symptoms brought on by consuming food and/or beverage: one (1) tablet 1 hour before eating.

A maximum of 2 tablets should be taken in 24 hours.

Health Canada has not authorized an indication for pediatric use. See 1.1 Pediatrics above.

### 4.4 Administration

Do not swallow tablet whole: chew completely.

## 5 OVERDOSAGE

There is no experience to date with deliberate overdosage. Doses of up to 800 mg/day famotidine have been employed in patients with pathological hypersecretory conditions with no serious adverse effects. In the event of overdosage, treatment should be symptomatic and supportive. Unabsorbed material should be removed from the gastrointestinal tract, the patient should be monitored, and supportive therapy should be employed.

Famotidine:
The oral $LD_{50}$ of famotidine in male and female rats and mice was >5000 mg/kg.

Calcium Carbonate:
Overdosage may result in hypercalcemia which may be associated with nausea, vomiting, constipation, mental status changes, lethargy, and weakness. Chronic overdose of calcium carbonate alone or with other calcium salts combined with alkali may result in milk-alkali syndrome, which presents typically with hypercalcemia, alkalosis, and renal dysfunction. Patients with renal insufficiency and renal failure may be predisposed to this condition.

Magnesium Hydroxide:
The oral ingestion of magnesium rarely results in toxicity in patients with normal renal function. Signs of hypermagnesemia typically begin to develop with plasma levels around 4 mEq/L (4.8 mg/dL). Symptoms generally correlate to magnesium blood levels; however, there is variability among literature reports in patients with similar blood levels.

Symptoms associated with blood levels between 4 and 10 mEq/L (4.8-12 mg/dL) include nausea, vomiting, flushing, somnolence, and hypotension. Symptoms that appear at or above plasma levels of 10 mEq/L (12 mg/dL) include ECG changes, loss of deep tendon reflex,

paralysis of voluntary muscle, and respiratory depression. Around 15 mEq/L (18 mg/dL) heart block and cardiac arrest may occur.

For management of a suspected drug overdose, contact your regional poison control centre.

## 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

**Table – Dosage Forms, Strengths, Composition and Packaging**

| Route of Administration | Dosage Form / Strength/Composition | Non-medicinal Ingredients |
|---|---|---|
| Oral | chewable tablet / famotidine 10 mg, calcium carbonate 800 mg and magnesium hydroxide 165 mg | cellulose acetate, crospovidone, dextrose monohydrate, flavours, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, mineral oil, Prosweet® Powder (contains cornstarch), sucralose |

Each PEPCID® COMPLETE® chewable tablet contains 10 mg famotidine, 800 mg of calcium carbonate, and 165 mg of magnesium hydroxide. Each tablet provides 320 mg of elemental calcium and 70 mg of elemental magnesium.

PEPCID® COMPLETE® chewable tablets (mint flavour) also contain FD&C Blue #1 and D&C Yellow #10. These tablets are round, with a concave centre, green-coloured tablets embossed with "P". Available in bottles of 25 and 50.

PEPCID® COMPLETE® chewable tablets (berry flavour) also contain D&C Red #7, FD&C Red #40 and FD&C Blue #1. These tablets are round, with a concave centre, purple-coloured tablets embossed with "P". Available in bottles of 25.

## 7 WARNINGS AND PRECAUTIONS

### General

In clinical trials with famotidine (PEPCID® AC), patients with other underlying acid gastrointestinal diseases (e.g., duodenal ulcer, gastric ulcer) did not experience complications; in general, they did not exhibit a clinically significant deterioration in their condition. However, if patients have difficulty or pain on swallowing, severe vomiting, black stool, choking, chest pain, or if abdominal discomfort persists, the underlying cause should be determined. Symptomatic response to therapy with PEPCID® COMPLETE® does not preclude the presence of gastric malignancy.

Patients with severe coexisting illness should consult a physician before commencing therapy with PEPCID® COMPLETE®.

Patients consuming nonsteroidal anti-inflammatory drugs may have dyspepsia as a side effect of these medicines and should consult a physician or a pharmacist before taking PEPCID® COMPLETE®.

Patients over 40 who are experiencing heartburn for the first time, and patients who have noticed unintentional weight loss should consult a physician before using the product.

Therapy should not exceed two weeks of continuous treatment without medical consultation.

**Driving and Operating Machinery**

Famotidine:
In very rare cases, some patients have experienced adverse reactions such as dizziness and somnolence while taking famotidine. Patients should be informed that they should avoid driving vehicles, operating machinery or doing activities which require prompt vigilance if they experience these symptoms (see 8 ADVERSE REACTIONS).

Calcium Carbonate and Magnesium Hydroxide:
Calcium carbonate and magnesium hydroxide has not been demonstrated to have effects on the ability to drive or use machines.

**Gastrointestinal**

Patients with a previous history of ulcer disease complications, those who are experiencing unintended weight loss in association with dyspeptic symptoms, and those who are middle-aged or older with new or recently changed dyspeptic symptoms should consult a physician before commencing therapy with PEPCID® COMPLETE®.

**Renal**

Patients with severe kidney disease should consult a physician before commencing therapy with PEPCID® COMPLETE®. A dosage adjustment may be necessary in patients with moderate or severe renal impairment (creatinine clearance less than 60 mL/min/1.48$m^2$). Magnesium is principally eliminated from the kidney, and the risk of developing hypermagnesemia is increased with impaired renal function. Oral calcium carbonate intake has occasionally been associated with milk alkali syndrome, and the risk of developing milk alkali syndrome is increased with impaired renal function.

Patients with pre-existing hypercalcemia or hypermagnesemia should consult a physician before using famotidine / antacid combination. Both magnesium and calcium are absorbed systemically following use of oral magnesium or calcium containing antacids, which could result in an increase in already raised blood calcium or magnesium levels.
See 10.3 Pharmacokinetics.

## 7.1 Special Populations

### 7.1.1 Pregnant Women

Famotidine:
Reproductive studies with famotidine have been performed in rats and rabbits at oral doses of up to 2000 and 500 mg/kg/day, respectively (approximately 2500 and 625 times the maximum recommended human prescription dose [80 mg] of famotidine, respectively), and have revealed no evidence of impaired fertility or harm to the fetus due to famotidine.

Calcium:
The maximum daily dose in case of pregnancy is 5000 mg of calcium carbonate (2000 mg of elemental calcium). Overconsumption of calcium carbonate as antacids or supplements may put pregnant women at risk for the possible development of milk-alkali syndrome, characterized by hypercalcemia, metabolic alkalosis, and acute kidney injury. Generally, it is considered that elemental calcium intake of 4000 mg/day can cause milk-alkali syndrome, but there have been some cases reporting its development in pregnant women who took >2000 mg/day of elemental calcium.

There are no adequate, well-controlled clinical studies in pregnancy for the combination of calcium carbonate, famotidine, and magnesium hydroxide. Since the safe use of PEPCID® COMPLETE® in pregnant women has not been established, pregnant women should not use PEPCID® COMPLETE® unless directed otherwise by a physician. This product should not be used during pregnancy unless the potential benefit of treatment to the mother outweighs the possible risks to the developing fetus.

### 7.1.2 Breast-feeding

Famotidine:
Famotidine is detectable in human milk. Breast-feeding mothers should either stop PEPCID® COMPLETE® or should stop breast-feeding.

Calcium Carbonate:
Excessive use of calcium-containing antacids should be avoided. Calcium can cross the placenta and is secreted in breast milk in significant amounts.

When taken as directed, calcium carbonate does not appear to adversely affect the mother or fetus. Maternal ingestion of calcium carbonate in labeled doses does not present at risk to the breast-feeding infant.

Magnesium Hydroxide:
There are no adequate or well-controlled studies of magnesium hydroxide in breast-feeding women. Magnesium hydroxide is acceptable to use while breast-feeding. Magnesium-containing emulsions administered orally to mothers did not affect the stools of breast-feeding infants.

### 7.1.3 Pediatrics

Safety and effectiveness in children have not been established. PEPCID® COMPLETE® should not be administered to children under 12 years of age.

### 7.1.4 Geriatrics

No dosage adjustment is required based on age (see 10.3 Pharmacokinetics).

## 8 ADVERSE REACTIONS

### 8.1 Adverse Reaction Overview

PEPCID® COMPLETE® (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg) has been demonstrated to be generally well tolerated.

### 8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

In primary studies (comparing PEPCID® COMPLETE®, antacid 21.5 mEq, famotidine 10 mg and placebo), PEPCID® COMPLETE® and the antacid groups (calcium carbonate/magnesium hydroxide 21 mEq) had similar proportions of patients with adverse experiences. The most common adverse experience was headache, occurring in 2.6% of patients receiving PEPCID® COMPLETE®.

### 8.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

**Clinical Trial Findings**

Changes in laboratory parameters have been observed with famotidine 10 mg.

Among the laboratory changes that were reported during clinical trials with PEPCID® AC were increases in AST, ALT, and WBC count, and decreases in hemoglobin and hematocrit. These changes were rarely of clinical significance. No famotidine-treated patients/subjects had to be discontinued from therapy because of laboratory adverse experiences.

### 8.5 Post-Market Adverse Reactions

During marketed use of prescription doses of famotidine, which are higher than those recommended for non-prescription use, the following adverse reactions have been reported; urticaria, liver enzymes abnormalities, cholestatic jaundice, anaphylaxis, angioedema, hypersensitivity, somnolence, dizziness, headache, abdominal discomfort and pain, abdominal

pain upper, diarrhea, dry mouth, nausea, vomiting, flatulence, oropharyngeal discomfort and pain, dysgeusia, pruritus, rash, malaise, asthenia, and fatigue. Toxic epidermal necrolysis has been reported very rarely with $H_2$-receptor antagonists.

The following adverse reactions have been reported; however, a causal relationship to therapy with PEPCID® has not been established: agitation, confusion, hallucinations, grand mal seizures, rare cases of impotence, thrombocytopenia, pancytopenia, leukopenia and agranulocytosis. Gynecomastia has been reported rarely. In most cases that were followed up, it was reversible after discontinuing treatment.

Adverse drug reactions (ADRs) identified from clinical trials and during postmarketing experience with famotidine/magnesium hydroxide/calcium carbonate are included in Table 1. The frequencies are provided according to the following convention:

Very common ≥1/10
Common ≥1/100 and < 1/10
Uncommon ≥1/1,000 and <1/100
Rare ≥1/10,000 and <1/1,000
Very rare <1/10,000
Not known (cannot be estimated from the available data)

**Table 1: Adverse Drug Reactions Identified During Post-Marketing Experience with Famotidine/Calcium Carbonate/Magnesium Hydroxide by Frequency Category Estimated from Spontaneous Reporting Rates***

| **System Organ Class**<br>Frequency Category | Adverse Event<br>Preferred Term (PT) |
|---|---|
| **Immune System Disorders** | |
| Very rare | Anaphylactic reaction |
| Very rare | Angioedema |
| Very rare | Hypersensitivity |
| Very rare | Urticaria |
| **Nervous System Disorders** | |
| Very rare | Somnolence** |
| Very rare | Dizziness |
| Very rare | Headache |

| **System Organ Class**<br>Frequency Category | Adverse Event<br>Preferred Term (PT) |
|---|---|
| **Gastrointestinal Disorders**<br>Very rare | <br>Abdominal discomfort<br>Abdominal pain<br>Abdominal pain upper<br>Diarrhea<br>Dry mouth**<br>Nausea**<br>Vomiting**<br>Flatulence***<br>Oropharyngeal discomfort<br>Oropharyngeal pain<br>Dysgeusia |
| **Skin and Subcutaneous Tissue Disorders**<br>Very rare<br>Very rare | <br>Pruritus<br>Rash |
| **General Disorders and Administration Site Conditions**<br>Very rare<br>Very rare<br>Very rare | <br>Malaise**<br>Asthenia**<br>Fatigue** |

*Patient exposure was estimated by calculation from sales data from IMS MIDAS™

**PT identified for famotidine 10mg/20mg

***PT identified for calcium carbonate/magnesium hydroxide

## 9 DRUG INTERACTIONS

### 9.2 Drug Interactions Overview

Studies with famotidine in man, in animal models, and in vitro have shown no significant interference with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds tested in man have included warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic blood flow and/or hepatic drug extraction has been tested and no significant effects have been found. Famotidine does not affect gastric alcohol dehydrogenase and, consequently, blood ethanol levels.

Concomitant administration of antacids can reduce the absorption of a variety of drugs, such as phenothiazines, benzodiazepines, and iron. Given the known drug-interaction profiles of the PEPCID® COMPLETE® components, no studies were conducted with PEPCID® COMPLETE® to directly characterize any potential interactions. Patients taking a prescription drug should

check with their pharmacist or physician before taking PEPCID® COMPLETE®. Most interactions can be avoided by taking PEPCID® COMPLETE® 2 hours before or after ingestion of other drugs.

### 9.4 Drug-Drug Interactions

Patients should consult a physician before using this product together with any of the following drugs:

Posaconazole Oral Suspension and Itraconazole:
Concomitant use of famotidine and magnesium hydroxide-containing antacids with the antifungal agents posaconazole oral suspension and itraconazole result in significantly reduced peak and trough plasma concentrations of posaconazole oral suspension and itraconazole, which may result in reduced antifungal efficacy.

Tyrosine Kinase Inhibitors (TKIs):
Co–administration of famotidine with the TKIs dasatinib, erlotinib, gefitinib, pazopanib may decrease plasma concentrations of TKIs resulting in lower efficacy, therefore co-administration of famotidine with these TKIs is not recommended. For further specific recommendations please refer to the product information of individual TKI medicinal products.

Calcium Carbonate:
The hypophosphatemic effect of calcium carbonate is attenuated with concomitant use of $H_2$-antagonists in patients undergoing chronic hemodialysis.

Tetracycline Hydrochloride; Doxycycline:
Magnesium hydroxide products may impair the absorption of certain orally administered antibiotics within the tetracycline group. The mechanism of action may be chelation with magnesium ions, resulting in the formation of a less soluble compound which is not readily able to penetrate the intestinal mucosa.

Penicillamine:
Magnesium-containing antacids may reduce the bioavailability of penicillamine through chelate formation.

Zinc Sulfate:
Calcium-containing antacids may reduce the bioavailability of zinc when administered as zinc sulfate, although the mechanism of this interaction is poorly understood.

Antiretroviral Medications:
Bio-availability of antiretroviral medications (e.g. integrase inhibitors such as Raltegravir Dolutegravir, Elvitegravir is significantly reduced by metal-cation containing antacids and dietary supplements.

Fluoroquinolones:
Fluoroquinolones, as a class, form chelates with multivalent cations, such as calcium. This reduction in bioavailability following chelate formation varies by agent, as does any recommendations for the separation of administration.

Calcium-containing antacids may reduce the bioavailability of fluoroquinolone antibiotics. Fluoroquinolones, as a class, form chelates with multivalent cations, such as calcium and magnesium. This reduction in bioavailability following chelate formation varies by agent, as does any recommendations for the separation of administration.

Minerals:
Calcium salts may decrease the absorption of iron and zinc. Consequently, iron, or zinc preparations should be taken one hour before or two hours after calcium carbonate or calcium carbonate-containing products.

Thiazide Diuretics:
Thiazide diuretics reduce the urinary excretion of calcium. Due to increased risk of hypercalcaemia, serum calcium should be regularly monitored during concomitant use of thiazide diuretics

### 9.5 Drug-Food Interactions

Interactions with food have not been established.

### 9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

### 9.7 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

## 10 CLINICAL PHARMACOLOGY

### 10.1 Mechanism of Action

Heartburn is a common symptom for which a variety of treatments exist. Single doses of antacid alone and histamine $H_2$-receptor antagonists (acid reducers) alone have been shown to relieve heartburn more effectively than placebo. Although both agents are believed to act by reducing intraluminal acidity, their mechanisms of action and pharmacodynamic profiles differ substantially.

Antacids are believed to provide a fast onset of action by neutralizing intraluminal acid on contact, but their duration of action is limited by physiologic clearing mechanisms. Histamine $H_2$-receptor antagonists inhibit gastric juice secretion, reducing acid and pepsin content, as well as the volume, of basal, nocturnal and stimulated gastric secretion. These acid reducers are believed to require a longer time to onset of effect than antacids, but these antagonists have an appreciably longer duration of action.

PEPCID® COMPLETE® (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg) contains both antacids (calcium carbonate and magnesium hydroxide) and an acid reducer, famotidine (an $H_2$-receptor antagonist).

*In Vitro* & Animal Data:
Famotidine is a specific, competitive, $H_2$-receptor antagonist. There was no effect *in vitro* on responses mediated by $H_1$-histamine, $beta_1$-adrenergic, or cholinergic receptors. Famotidine was inactive in radioligand binding to dopaminergic, neuroleptic, serotonergic, adrenergic, cholinergic, and purinergic sites. Famotidine was also inactive in an androgen receptor assay.

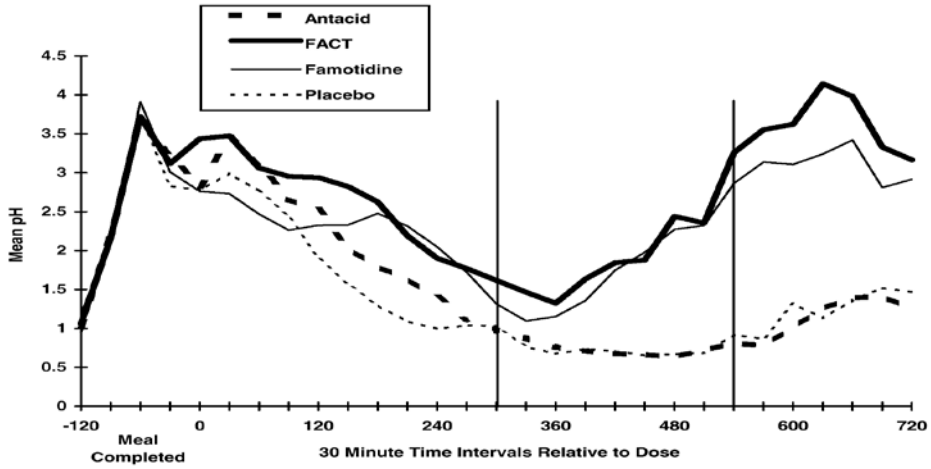
The interaction between famotidine and $H_2$-receptors is tissue-dependent. In guinea pig lungs and rabbit gastric glands the effects of famotidine were surmountable and readily reversible on washout, indicating classic competitive inhibition at the $H_2$-receptor sites. However, in guinea pig atria, famotidine acted as a non-competitive $H_2$ antagonist, and recovery after washout of famotidine was retarded.

### 10.2 Pharmacodynamics

In a clinical study to determine the pharmacodynamic profile of PEPCID® COMPLETE®, esophageal and gastric pH were measured following administration of either PEPCID® COMPLETE®, famotidine 10 mg, antacid (calcium carbonate/magnesium hydroxide 21 mEq) or placebo.

Figure 1 displays gastric pH by treatment from 2 hours prior to dosing to 12 hours postdose. During 5- to 9-hours postdose, the mean intragastric pH was significantly greater with PEPCID® COMPLETE® and famotidine treatments than with the antacid (calcium carbonate/magnesium hydroxide 21 mEq) and placebo. The mean intragastric pH for the antacid and placebo treatments were similar during the 5- to 9-hour postdose period. These results demonstrate the longer duration of effect on gastric pH of the acid reducer and PEPCID® COMPLETE® over the antacid.

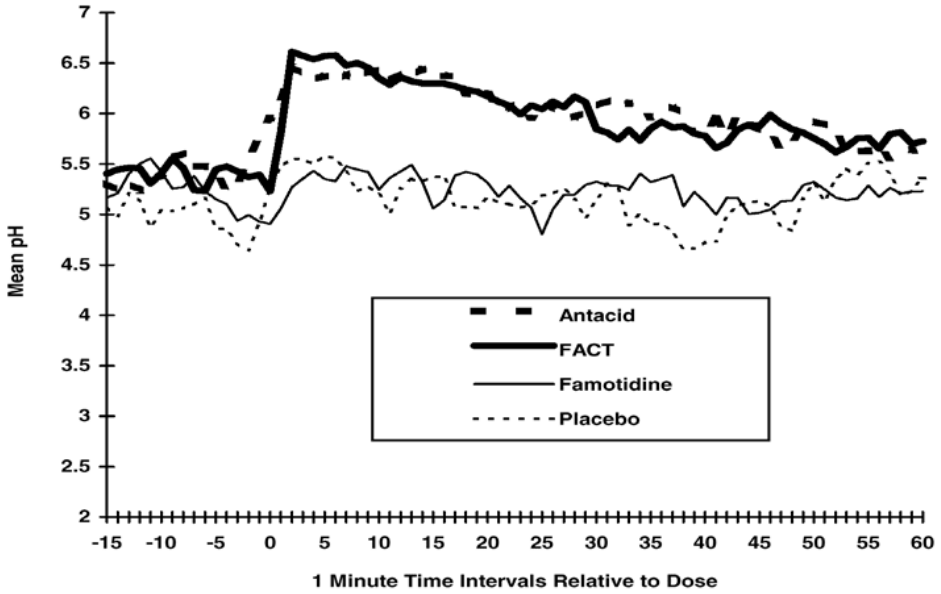
**Figure 1: Gastric pH Means at 30-Minute Time Intervals Relative to Dosing (n = 23)**




FACT= famotidine antacid combination tablet (famotidine 10 mg, antacid 21 mEq)
Famotidine = famotidine 10 mg film-coated tablet
Antacid = calcium carbonate/magnesium hydroxide 21 mEq

Figure 2 displays mean esophageal pH by treatment from 15 minutes prior to dosing to 60 minutes postdose. Compared to famotidine and placebo, mean intraesophageal pH was significantly greater in the PEPCID® COMPLETE® and antacid groups during the first hour. These results demonstrate that PEPCID® COMPLETE® and the antacid have a faster onset of effect on esophageal pH than the acid reducer (famotidine 10 mg).

**Figure 2: Esophageal pH Means at 1-Minute Time Intervals Relative to Dose: 0 to 60 Minutes Postdose (n= 23)**




FACT= famotidine antacid combination tablet (famotidine 10 mg, antacid 21 mEq)
Famotidine = famotidine 10 mg film-coated tablet
Antacid = calcium carbonate/magnesium hydroxide 21 mEq

This study shows that the pharmacodynamic profile of PEPCID® COMPLETE® reflects the action of both the antacid and acid reducer components. The PEPCID® COMPLETE® combination tablet has a faster onset of effect on esophageal pH than the acid reducer and a longer duration of effect on gastric pH than the antacid.

These results are consistent with clinical data, obtained from three studies, demonstrating the onset and duration benefits of PEPCID® COMPLETE® in heartburn relief. According to the data, PEPCID® COMPLETE® relieved heartburn significantly longer than the antacid and significantly faster than the acid reducer.

Animal Data:
Famotidine inhibits gastric secretion evoked by histamine and other secretagogues. In dogs, the $ED_{50}$ was 0.03 mg/kg after oral or intravenous administration of famotidine. An oral dose of 2.1 mg/kg in dogs inhibited gastric secretion for at least 24 hours. An oral dose of 3 mg/kg one hour prior to feeding inhibited the acid response in dogs during a 4-hour post feeding period by an average of 96%.

Gastrointestinal Effects other than Antisecretory – Famotidine prevented gastric erosions induced in rats by cold restraint, water immersion, pyloric ligation, or drugs such as acetylsalicylic acid, histamine or prednisolone; also, duodenal ulcers caused by cysteamine and

mepirizole. It also significantly accelerated the healing of the gastric lesions induced by acetic acid and the duodenal ulcers produced by mepirizole.

The antiulcer effect of famotidine, plus magnesium and aluminum hydroxides was greater than the sum of the effects of these drugs used separately.

Famotidine inhibited the gastric lesions and hemorrhage resulting from blood removal and histamine injection in anesthetized rats.

In normal rats, famotidine had no effect on the concentration of gastric mucosal histamine, but it did reduce the levels of cAMP, particularly in response to histamine stimulation.

In anaesthetized cats, famotidine had no effect on the intragastric electropotential when tested at intragastric doses more than ten-fold greater than those required to block gastric secretion maximally.

Systemic pharmacologic effects of famotidine involving the CNS, cardiovascular, respiratory or endocrine systems have not been found to date.

Cardiorenal Effects – The cardiorenal effects of famotidine were studied in dogs and rats. Ten mg/kg of famotidine administered orally were without effect on the blood pressure of spontaneously hypertensive rats. In anaesthetized dogs, intravenous administration of 1.0 and 4.0 mg/kg of famotidine was without effect on cardiovascular parameters relating to the autonomic nervous system, blood pressure, heart rate, or respiratory function. In conscious dogs, an oral dose of 10 mg/kg was without diuretic effect.

Central Nervous System Effects – The effects of famotidine on the central nervous system were studied in squirrel monkeys, mice, and cats. In monkeys, famotidine had a bidirectional effect on lever pressing (avoidance response) causing an increase at the low dose (1.0 mg/kg p.o.) and a small decrease at 9 mg/kg. In mice following intraperitoneal administration of 6 to 150 mg/kg no overt behavioral signs or symptoms of central nervous system activity were observed. In mice famotidine was not active as an antagonist of the CNS actions of TRH, neurotensin, substance P, or amphetamine. Famotidine was free of major or minor tranquilizing, anticonvulsant, anticholinergic, ganglionic blocking, or dopaminergic activity. In cats, famotidine did not affect the EEG or arousal response but did prolong the duration of hippocampal after-discharge. Only 4% of the plasma concentration of the drug was detected in the cerebrospinal fluid.

### 10.3 Pharmacokinetics

**Absorption:**
Famotidine is incompletely absorbed.

Animal Data:
The absorption, distribution, metabolism and excretion of famotidine were studied in two animal species. Absorption was 28% in the rat and 43% in the dog.

**Distribution:**
The bioavailability of oral doses is 40-45%. Bioavailability of famotidine may be slightly increased by food; however, this effect is of no clinical significance.

Animal Data:
The plasma half-life in dogs was 2.5 hours, which was unchanged after repeated doses, indicating no tendency for the drug to accumulate. In rats, the highest levels of radioactivity after an oral dose of famotidine were found in the gastrointestinal tract, kidneys, liver, submandibular glands, arteries, epiphyseal membrane, fascia, and uvea. The distribution pattern was not affected on repeated dosing. Famotidine did not effectively cross the blood-brain or placental barrier of rats. It was present in rat milk.

**Metabolism:**
Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. $C_{max}$ values of 37.13 ng/mL and 38.57 ng/mL for the famotidine/antacid combination tablet (famotidine 10 mg, calcium carbonate/ magnesium hydroxide 21 mEq) (PEPCID® COMPLETE®) and the famotidine 10 mg film-coated tablet (PEPCID® AC), respectively, were found in one bioequivalence study.

Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of famotidine in plasma is protein bound.

*In Vitro* & Animal Data:
The only metabolite of famotidine in rat and dog urine was the sulfoxide derivative, which was present in minor amounts.

Effects on Liver Microsomal Drug-Metabolizing Enzymes – Famotidine did not affect pentobarbital or hexobarbital sleeping times and it did not affect ascorbic acid excretion, suggesting that famotidine does not induce drug-metabolizing enzymes. Famotidine caused none of the changes induced by cimetidine on the pharmacokinetics of diazepam, warfarin, and propranolol. Famotidine produced only minimal suppression of aminopyrine and diazepam N-demethylase activity *in vitro* and showed little affinity for testosterone hydroxylases of mouse liver *in vitro*.

**Elimination**
Famotidine has an elimination half-life of 2.5-3.5 hours. Famotidine is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450 mL/min., indicating some tubular excretion.

Twenty-five to 30% of an oral dose and 65-70% of an intravenous dose are recovered in the urine as unchanged compound. The only metabolite identified in man is the S-oxide. There is a close relationship between creatinine clearance values and the elimination half-life of famotidine.

Magnesium hydroxide and calcium carbonate are cleared from the empty stomach in about 30 minutes. Food prolongs the neutralizing effects of these compounds for about 2 hours.

Calcium carbonate and magnesium hydroxide are incompletely absorbed, and unreacted insoluble antacids are eliminated in the feces. When the products from the reacted antacids enter the intestines, some of the cations are absorbed.

$Mg^{2+}$ is eliminated in the feces as $Mg(OH)_2$ and as soluble salts, such as the chloride and bicarbonate. Small amounts of the cations from the insoluble antacids are eliminated as soaps, phosphates, and other insoluble compounds. The chronic ingestion of antacid doses of magnesium hydroxide causes only slight increases in plasma concentrations of $Mg^{2+}$ in persons with normal renal function.

The fraction of $Ca^{2+}$ absorbed from $CaCO_3$ averages 15% in normal patients, causing a transient hypercalcemia.

$Ca^{2+}$ absorption varies in proportion to gastric acid secretion. A dose-absorption relationship has not been established for $CaCO_3$; however, by analogy with other forms of $Ca^{2+}$, the amount absorbed probably reaches a plateau at a dose of about 20 g of $Ca^{2+}$ per day. Dietary factors and certain hormones alter the absorption of $Ca^{2+}$.

Some $Ca^{2+}$ will be excreted as insoluble phosphates and soaps. Elimination of absorbed $Ca^{2+}$ is mainly by urinary excretion, which varies with the creatinine clearance.

Animal Data:
Urinary and fecal excretion of radioactivity in rats accounted for 28% and 70%, respectively, of an oral dose, compared to 83% and 17% respectively, of an intravenous dose. About 2.4% of the dose in rats was excreted in the bile. Dogs excreted 45% of an oral dose in the urine, compared to 100% of an intravenous dose.

**Special Populations and Conditions**

- **Geriatrics:** In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of famotidine.
- **Sex:** Serum prolactin levels do not rise after intravenous bolus doses of 20 mg of famotidine and no antiandrogenic effects have been detected.
- **Renal Insufficiency:** In patients with severe renal insufficiency, i.e., creatinine clearance less than 10 mL/min., elimination half-life of famotidine may exceed 20 hours (see 4 DOSAGE AND ADMINISTRATION)**.**

  Since renal excretion is the principal route of elimination, toxic concentrations may occur in persons with renal failure (see 4 DOSAGE AND ADMINISTRATION).

  Although transient hypercalcemia is not a problem in normal patients, as little as 3 to 4 g per day can be problematic in patients with uremia. However, this is well above the maximum daily dose of CaCO3 provided by PEPCID® COMPLETE® (1.6 g per day).

## 11 STORAGE, STABILITY AND DISPOSAL

Store at 15°C - 30°C. Protect from moisture.

**PART II: SCIENTIFIC INFORMATION**

## 13 PHARMACEUTICAL INFORMATION

**Drug Substance**

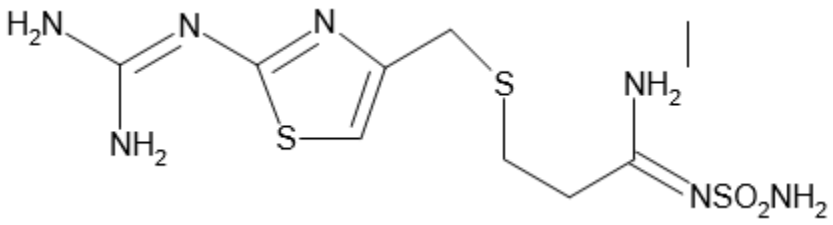
**A. Famotidine**

Proper name: famotidine

Chemical name: N'-(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio] Propanimidamide

Molecular formula and molecular mass: $C_8H_{15}N_7O_2S_3$ / 337.44

Structural formula:




Physicochemical properties: Famotidine is a white to pale yellow crystalline compound that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water and practically insoluble in ethanol.

**B. Calcium Carbonate**

Molecular formula and molecular mass: $CaCO_3$ / 100.09

**C. Magnesium Hydroxide**

Molecular formula and molecular mass: $Mg(OH)_2$ / 58.32

## 14 CLINICAL TRIALS

### 14.1 Trial Design and Study Demographics

In a double-blind, randomized, parallel-group, multiple-dose study comparing PEPCID® COMPLETE® to famotidine 10 mg, antacid (calcium carbonate/magnesium hydroxide 21 mEq) and placebo in patients with frequent heartburn, the adequacy of relief was assessed at 15-minute intervals for the first hour post-dose, then hourly for 8 hours postdose.

### 14.2 Study Results

Table 2 shows the number of heartburn episodes each patient recorded with adequate relief first occurring at each time point within 2 hours. Heartburn treated with PEPCID® COMPLETE® was statistically more likely to achieve adequate relief at an earlier time point than episodes treated with the acid reducer, famotidine 10 mg (p= 0.011). Heartburn episodes for PEPCID®

COMPLETE® patients were also more likely to achieve adequate relief at an earlier time point than episodes for the antacid (calcium carbonate/magnesium hydroxide 21 mEq) and placebo patients, respectively (p= 0.042 and p< 0.001).

**Table 2 – Onset Data: Number (Cumulative %) of Heartburn Episodes Adequately Relieved (N=1231)**

| Relief at | FACT n = 305 Tot Eps* = 1205 | | Famotidine 10 mg FCT n = 311 Tot Eps* = 1229 | | Antacid 21 mEq n = 308 Tot Eps* = 1212 | | Placebo N = 307 Tot Eps* = 1217 | |
|---|---|---|---|---|---|---|---|---|
| | n | cum %** | n | cum %** | n | cum %** | n | cum %** |
| 15 mins | 322 | 27.0 | 249 | 20.3 | 301 | 25.1 | 191 | 15.7 |
| 30 mins | 222 | 45.3 | 215 | 37.8 | 190 | 40.9 | 210 | 33.0 |
| 45 mins | 234 | 64.6 | 257 | 58.6 | 200 | 57.4 | 262 | 54.4 |
| 60 mins | 172 | 78.8 | 190 | 73.9 | 159 | 70.5 | 203 | 71.2 |
| 120 mins | 77 | 85.3 | 94 | 81.5 | 102 | 78.8 | 77 | 77.5 |
| >120 mins | 178 | 100.0 | 224 | 100.0 | 260 | 100.0 | 274 | 100.0 |

*Eps = episodes
**Cumulative percentages based on the number of episodes
FACT: famotidine antacid combination tablet
FCT: film-coated tablet
Antacid: calcium carbonate/magnesium hydroxide 21 mEq

Results presented in Table 3 show that, in this same study, PEPCID® COMPLETE® produces a statistically longer duration of adequate relief than the antacid. The proportion of episodes relieved for at least 7 hours was greater with PEPCID® COMPLETE® than antacid (p= 0.001) and placebo (p< 0.001).

**Table 3 – Duration Data: Number (Cumulative %) of Heartburn Episodes Adequately Relieved (N=1231)**

| Adequate Relief for: | FACT n = 305 Tot Eps* = 1205 | | Famotidine 10 mg FCT n = 311 Tot Eps* = 1229 | | Antacid 21 mEq n = 308 Tot Eps* = 1212 | | Placebo N = 307 Tot Eps* = 1217 | |
|---|---|---|---|---|---|---|---|---|
| | n | cum %** | n | cum %** | n | cum %** | n | cum %** |
| ≥ 7 hours | 845 | 70.4 | 842 | 68.3 | 741 | 61.3 | 718 | 59.0 |
| 6 hours | 20 | 72.0 | 19 | 69.8 | 14 | 62.4 | 22 | 60.8 |
| 5 hours | 28 | 74.3 | 29 | 72.2 | 30 | 64.9 | 43 | 64.3 |
| 4 hours | 26 | 76.5 | 31 | 74.7 | 41 | 68.2 | 48 | 68.2 |
| < 4 hours | 152 | 89.0 | 142 | 86.2 | 180 | 83.2 | 182 | 83.2 |
| No onset | 134 | 100.0 | 166 | 100.0 | 206 | 100.0 | 204 | 100.0 |

*Eps = episodes
**Cumulative percentages based on the number of episodes
FACT: famotidine antacid combination tablet
FCT: film-coated tablet
Antacid: calcium carbonate/magnesium hydroxide 21 mEq

### 14.3 Comparative Bioavailability Studies

Three single-dose, two-period crossover studies in healthy volunteers were conducted to characterize the bioavailability of famotidine administered as PEPCID® COMPLETE®, referred to in the studies as FACT -- famotidine/antacid combination tablet (famotidine 10 mg, calcium carbonate/ magnesium hydroxide 21 mEq). The following table summarizes the mean pharmacokinetic parameters in these studies.

**Table 4 – Summary of Results of Pharmacokinetic Analysis**

| Pharmacokinetic Measure | Protocol 095 N = 24, Fed [Ref. C-2] | | Protocol 101 N = 24, Fasted [Ref. C-5] | | Protocol 097 N = 12, Fasted [Ref. C-3] | |
|---|---|---|---|---|---|---|
| | FACT | FCT | FACT | FCT | FACT | I.V. |
| $AUC_{0\text{-}24\ hr}$ ng·h/ml (geometric mean) | 252.1 | 243.8 | 277.8 | 296.7 | 228.6 | 429.3 |
| Ratio (FACT/FCT) | 1.03 | - | 0.94 | - | 0.53‡ | - |
| 90% CI (FACT/FCT) | 0.99, 1.09 | - | 0.87, 1.01 | - | 0.48, 0.60‡ | - |
| $C_{max}$ ng/ml (geometric mean) | 37.1 | 38.6 | 49.8 | 53.8 | 37.7 | - |
| Ratio (FACT/FCT) | 0.96 | - | 0.93 | - | - | - |
| 90% CI (FACT/FCT) | 0.91, 102 | - | 0.84, 1.02 | - | - | - |
| $T_{max}$ hr (arithmetic mean) | 2.9 | 2.9 | 2.4 | 1.8 | 2.5 | - |
| Arithmetic mean difference (FACT vs FCT) | 0.04 | - | 0.53 | - | - | - |
| 90% CI (arithmetic mean difference) | -0.26,0.33 | - | 0.11, 0.94 | - | - | - |

†Analysis based on an ANOVA model appropriate for two-period crossover design
‡Geometric mean ration and 90% CI of $AUC_{0\text{-}24\ hr}$ (FACT/I.V.)
FACT: famotidine antacid combination tablet (famotidine 10 mg, calcium carbonate / magnesium hydroxide 21 mEq)
FCT: film-coated tablet
I.V. = intravenous

Overall, these data indicate that there is no clinically meaningful difference between PEPCID® COMPLETE® and PEPCID® AC film-coated tablets (famotidine 10 mg) with respect to extent or rate of absorption of famotidine.

In both normal volunteers and hypersecretors, famotidine inhibited basal nocturnal and daytime gastric secretion, as well as secretion stimulated by a variety of stimuli, such as pentagastrin and food.

After oral administration, a dose-response relationship was clearly demonstrated from 0.5 and 10 mg famotidine in terms of raising gastric pH between and after meals. Famotidine doses of 2.5 to 10 mg were demonstrated to produce a statistically significant effect on gastric pH as compared to placebo. The onset of effect for the 5 and 10 mg doses was seen at approximately 1.5 hours postdose while that of the 2.5 mg dose was not seen until 2.5 hours postdose. The maximum effect, as measured by peak mean pH value, occurred at 3.5 hours. The activity of the 5 and 10 mg doses continued until approximately 9 hours postdose. Famotidine was well- tolerated at these dose levels.

Fasting and postprandial serum gastrin levels may be slightly elevated during periods of drug antisecretory effect, and with chronic therapy an increase in gastric bacterial flora may occur. Gastric emptying and exocrine pancreatic function are not affected by famotidine.

## 15 MICROBIOLOGY

No microbiological information is required for this drug product.

## 16 NON-CLINICAL TOXICOLOGY

**General Toxicology:**

Acute Toxicity:

| Species | Sex | Route | $LD_{50}$ (mg/kg) |
|---|---|---|---|
| Mouse | M | P.O.[x] | 4684 |
| | F | P.O.[x] | 3233 |
| Mouse | M | I.V. (4%) | 254 |
| | F | I.V. (4%) | 358 |
| Rat | M | P.O.[x] | 4907 |
| | F | P.O.[x] | 4049 |
| Rat | M | I.P. | 987 |
| | F | I.P. | 814 |

[x]In solution (acidic, 50-55$^{o}$C deonized water)
I.V. = intravenous; I.P. = intraperitoneal; P.O. = oral

Subacute and Chronic Toxcity:
Famotidine is well tolerated by both rats and dogs at doses of 2 g/kg twice a day orally in subacute studies and at doses up to 1000 or 2000 mg/kg/day for one year in these species. Eosinophilic cytoplasmic granularity of gastric chief cells was seen at a higher incidence in rats given 200 mg/kg/day or more of the compound compared to controls. This is considered as a secondary effect due to the exaggerated pharmacologic activity of the compound and at these extremely high dosage levels and is considered of no toxicologic significance. In a 106-week study in rats designed to study the carcinogenic potential of the compound, this gastric change did not progress to hyperplasia or neoplasia. Similarly, mice (given the compound for 92 weeks) showed no evidence of a neoplastic potential. Based on the results from studies performed using pharmacologically-related compounds, this change was fully reversible.

Intravenous administration of famotidine was well tolerated by rats for 13 weeks at dosage levels of up to 20 mg/kg/day and by dogs, except for occasional emesis, at dosage levels of up to 10 mg/kg/day for 5 to 26 weeks.

Magnesium hydroxide was well tolerated in acute toxicity studies. It did not produce toxic effects in rats at doses of 1000 mg/kg/day in combined repeated and reproductive toxicity study.

Calcium Carbonate has low acute toxicity in rats and mice. The repeat dose toxicity studies in animals did not show adverse effects at therapeutic doses.

**Carcinogenicity:** A 92-week oral carcinogenicity study was conducted in mice at famotidine doses of 20, 200 and 2000 mg/kg/day. No evidence of a carcinogenic potential was seen. A 106-week oral carcinogenicity study in rats given doses of 20, 200 and 2000 mg/kg/day did not reveal any carcinogenic potential for famotidine.

No carcinogenic data on magnesium hydroxide was reported in published literature. However, mice fed magnesium chloride for 96 weeks showed no carcinogenic potential.

There is no non-clinical data available. However, calcium carbonate is unlikely to have carcinogenic potential as both calcium and carbonate are natural constituents of cellular systems in humans.

**Genotoxicity:** Famotidine was tested in a reverse-mutation test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with and without metabolic activation. No mutagenic potential was seen. These same studies were performed with famotidine/sodium, nitrite reaction mixture and C-nitroso derivatives of famotidine and they were also negative. Famotidine and C-nitroso derivatives of famotidine were tested in the rec-assay using *Bacillus subtilis* H17 and M45 and the tests were negative for DNA-damaging capacity of the compounds. In in vivo studies in mice, a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was seen.

Magnesium hydroxide was reported to be non-genotoxic in *in-vitro* mutagenic assays.

Calcium carbonate is reported to be non-mutagenic and non-clastogenic in *in vitro* genotoxicity assays.

**Reproductive and Developmental Toxicology:** In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day (approximately 2500 and 250 times the maximum recommended prescription human dose, respectively), fertility and reproductive performance were not affected. Famotidine given orally to pregnant rats up to 2000 mg/kg/day or intravenously at dosage levels up to 200 mg/kg/day, from Days 7 to 17 of pregnancy did not reveal any evidence of embryolethality or teratogenicity.

Oral administration of famotidine to pregnant rabbits from Days 6 to 18 of pregnancy at dosage levels up to 500 mg/kg/day revealed no evidence of embryolethality or teratogenicity.

Magnesium hydroxide did not cause any teratogenic or developmental effects in rats in a combined repeated and reproductive/developmental screening test up to 1000 mg/kg/day.

Calcium carbonate is not teratogenic at the highest dose of 1562 mg/kg/day in rats. Calcium carbonate did not show any fertility effects at a highest tested dose of 1000 mg/kg/day in rats. The preclinical evidence does not indicate a fertility impairment risk to humans.

**Special Toxicology:** The effects of famotidine on the thyroid of rats were evaluated after five weeks of oral administration at doses up to 2000 mg/kg/day. No evidence of treatment-

related alterations of serum thyroid hormone levels, thyroid weight or the microscopic appearance were seen after administration of famotidine.

In immunogenicity studies, no effect on the production of IgE antibodies was seen in the sera of mice which were injected, once intraperitoneally, with famotidine alone (up to 2 mg/ 8 mL/kg) or coupled with either mouse serum albumin or ovalbumin. The sera were used to measure passive cutaneous anaphylaxis in rats which were then challenged with solutions of antigens similar to those antigens used for the initial dose in mice. Similarly, no evidence of an anaphylactic reaction was seen in guinea pigs challenged intravenously with famotidine after initiating doses (three times, subcutaneously, at six-day intervals) of up to 10 mg/mL.

**PATIENT MEDICATION INFORMATION**

**READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE**

**PEPCID® COMPLETE®**

**Famotidine / Calcium Carbonate / Magnesium Hydroxide Chewable Tablets**

Read this carefully before you start taking **PEPCID® COMPLETE®** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **PEPCID® COMPLETE®**.

## What is PEPCID® COMPLETE® used for?

- Begins to work on contact to provide fast, long lasting and effective relief from heartburn, acid indigestion and upset or sour stomach due to excess stomach acid.
- Prevents these symptoms brought on by consuming food and/or beverage.

## How does PEPCID® COMPLETE® work?

PEPCID® COMPLETE® contains the active ingredient famotidine (an acid reducer) along with the antacids, calcium carbonate and magnesium hydroxide. This advanced formula combines the benefits of both an antacid and acid reducer in one tablet.

PEPCID® COMPLETE® combines these two types of ingredients because they relieve heartburn in two different ways. The antacid begins by neutralizing acid on contact. The acid reducer keeps working, day or night, to reduce the production of excess stomach acid.

## What are the ingredients in PEPCID® COMPLETE®?

Medicinal ingredients: famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg

Non-medicinal ingredients: cellulose acetate, crospovidone, dextrose monohydrate, flavours, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, maltodextrin, mineral oil, Prosweet® Powder (contains cornstarch), sucralose

PEPCID® COMPLETE® chewable tablets – mint flavour also contains FD&C Blue #1 and D&C Yellow #10.

PEPCID® COMPLETE® chewable tablets – berry flavour also contains D&C Red #7, FD&C Red #40 and FD&C Blue #1.

**PEPCID® COMPLETE® comes in the following dosage forms:**

Chewable tablet

**Do not use PEPCID® COMPLETE® if:**

- you are allergic to famotidine, calcium carbonate, magnesium hydroxide or any nonmedicinal ingredients (see What are the ingredients in PEPCID® COMPLETE®?) in the product
- if you have had an allergic reaction to another product that contains an acid reducer (e.g. ranitidine)
- with other acid reducers

**To help avoid side effects and ensure proper use, talk to your healthcare professional before you take PEPCID® COMPLETE®. Talk about any health conditions or problems you may have, including if you:**

- are pregnant or breast-feeding
- have difficulty or pain on swallowing, severe vomiting, black stool, choking, or persistent stomach pains/discomfort
- have kidney disease as you may need a dosage adjustment
- have any other severe illnesses
- are over 40 years of age and are experiencing new or recently changed symptoms of acid indigestion or heartburn
- are taking any prescription or over-the-counter medications, such as nonsteroidal anti-inflammatory drugs [NSAIDs] (because these medicines may be causing your symptoms)
- have a previous history of ulcer disease complications
- are experiencing unintended weight loss in association with your symptoms of acid indigestion or heartburn
- have heartburn over 3 months as this may be a sign of a more serious condition
- have heartburn with light headedness, sweating and dizziness
- have chest or shoulder pain with shortness of breath; sweating; pain spreading to arms, neck or shoulders; or light headedness

**Other warnings you should know about:**

Stop use and ask a doctor if:

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

Pepcid® Complete® is not expected to affect your ability to drive or operate machinery. However, if tiredness or dizziness occur, you should not drive or use machines.

**Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.**

**The following may interact with PEPCID® COMPLETE®:**

- prescription drugs
- iron, calcium carbonate or zinc sulfate
- posaconazole oral suspension and itraconazole (for fungal infection)
- penicillamine
- tetracycline hydrochloride, doxycycline, fluoroquinolones (antibiotics) or drugs for HIV
- minerals
- thiazide diuretics (water pills)
- most of the tyrosine kinase inhibitors: dasatinib, erlotinib, gefitinib, pazopanib (to treat cancers)"

Most interactions can be avoided by taking PEPCID® COMPLETE® 2 hours before or after ingestion of other drugs.

**How to take PEPCID® COMPLETE®:**

- Do not swallow tablet whole: chew completely
- Do not take within two hours of another medicine because the effectiveness of the other medicine may be altered
- If symptoms get worse or persist for more than two consecutive weeks, or if new symptoms develop, stop use and consult your doctor

**Usual dose:**

**For Heartburn or Acid Indigestion:** Adults and children 12 years and older: For fast, long lasting and effective relief of symptoms, chew one (1) tablet. If symptoms return, you may chew another tablet. For prevention of acid-related symptoms brought on by consuming food and/or beverage, chew one (1) tablet 1 hour before eating. Maximum 2 tablets in 24 hours.

**What Else Can Be Done to Avoid Symptoms**

- Do not lie down soon after eating.
- If you are overweight, lose weight.
- If you smoke, stop or cut down
- Avoid or limit foods such as caffeine, chocolate, fatty foods, spicy foods and alcohol
- Do not eat just before bedtime

**Overdose:**

If you think you, or a person you are caring for, have taken too much PEPCID® COMPLETE®, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

**What are possible side effects from using PEPCID® COMPLETE®?**

PEPCID® COMPLETE® is generally well tolerated.

| Serious side effects and what to do about them | | | |
|---|---|---|---|
| **Symptom / effect** | **Talk to your healthcare professional** | | **Stop taking drug and get immediate medical help** |
| | **Only if severe** | **In all cases** | |
| **VERY RARE** | | | |
| Dizziness, headache, sleepiness, weakness | ✓ | | |
| Stomach pain, diarrhea, dry mouth, nausea, vomiting | | ✓ | |
| Allergic reactions such as hives, rash, swelling, itching and difficulty breathing | | ✓ | |

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

**Reporting Side Effects**

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**Storage:**

Store tablets at 15°C - 30°C. Protect from moisture.

Keep out of reach and sight of children.

**If you want more information about PEPCID® COMPLETE®:**

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pepcid.ca, or by calling 1-800-4PEPCID.

This leaflet was prepared by McNeil Consumer Healthcare, division of Johnson and Johnson Inc.

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