PRODUCT MONOGRAPH

PEPCID® COMPLETE®

(famotidine 10 mg, calcium carbonate 800 mg and
magnesium hydroxide 165 mg tablets)

Chewable Tablets

Combination Histamine H_2-Receptor Antagonist and Antacid

McNeil Consumer Healthcare,
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(famotidine, calcium carbonate and magnesium hydroxide)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Chewable Tablet / famotidine 10 mg, calcium carbonate 800 mg and magnesium hydroxide 165 mg	*For a complete listing see Dosage Forms, Composition and Packaging section.*

INDICATIONS AND CLINICAL USE

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.

CONTRAINDICATIONS

- Patients who are hypersensitive to this drug or to any ingredient in the formulation or component of the container.
- 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.

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.

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/1.48m^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 ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics).

Special Populations

Pregnant Women: 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. There are, however, no adequate or well-controlled studies in pregnant women with famotidine.

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.

Nursing Women: Famotidine is detectable in human milk. Nursing mothers should either stop PEPCID® COMPLETE® or should stop nursing.

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.

Geriatrics: No dosage adjustment is required based on age (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Excretion).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

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

Abnormal Hematologic and Clinical Chemistry 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.

Post-Market Adverse Drug 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.

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.

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

Itraconazole

Concomitant use of famotidine and magnesium hydroxide-containing antacids with the antifungal agent itraconazole results in significantly reduced peak and trough plasma concentrations of itraconazole, which may result in reduced antifungal efficacy.

Calcium carbonate

The hypophosphatemic effect of calcium carbonate is attenuated with concomitant use of H2-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.

Ciprofloxacin

Calcium- or magnesium-containing antacids may reduce the bioavailability of ciprofloxacin through chelate formation.

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.

DOSAGE AND ADMINISTRATION

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 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.

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.

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.

ACTION AND CLINICAL PHARMACOLOGY

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.

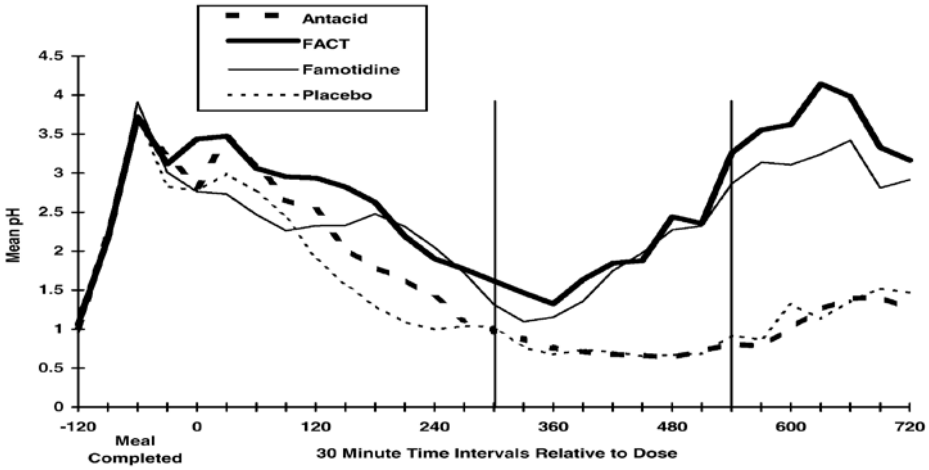
PEPCID® COMPLETE® (famotidine 10 mg, calcium carbonate 800 mg, magnesium hydroxide 165 mg) contains both antacids (calcium carbonate and magnesium hydroxide) and an acid reducer, famotidine (an H_2-receptor antagonist).

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)



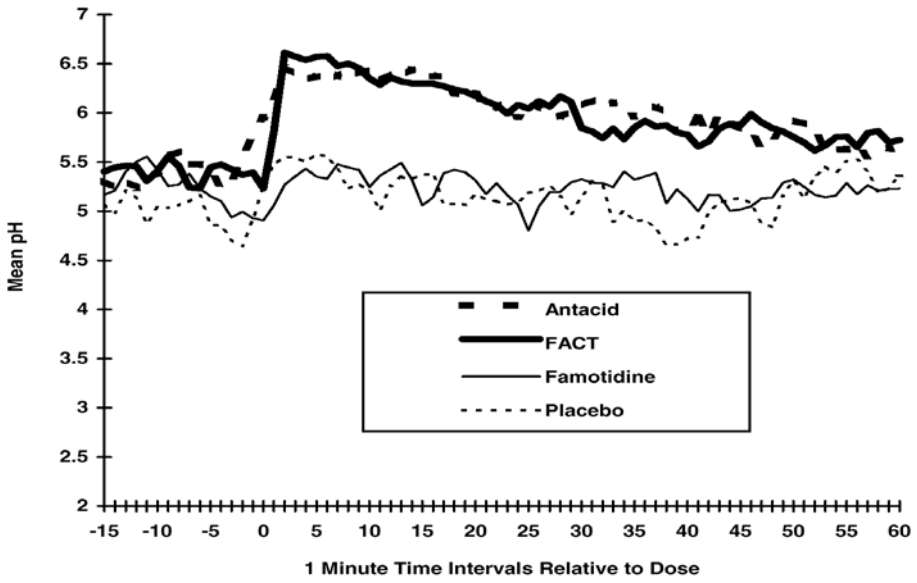
FACT= famotidine antacid combination tablet (famotidine 10 mg, antacid 21 mEq)

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.

Pharmacokinetics

Absorption: Famotidine is incompletely absorbed.

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.

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.

Excretion: 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. 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 DOSAGE AND ADMINISTRATION). In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics 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. Since renal excretion is the principal route of elimination, toxic concentrations may occur in persons with renal failure (see DOSAGE AND ADMINISTRATION).

The fraction of Ca^{2+} absorbed from $CaCO_3$ averages 15% in normal patients, causing a transient hypercalcemia. Although 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 $CaCO_3$ provided by PEPCID® COMPLETE® (1.6 g per day).

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 unsoluble phosphates and soaps. Elimination of absorbed Ca^{2+} is mainly by urinary excretion, which varies with the creatinine clearance.

STORAGE AND STABILITY

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

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 also contain the following 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 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.

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance
A. Famotidine

Proper name: famotidine

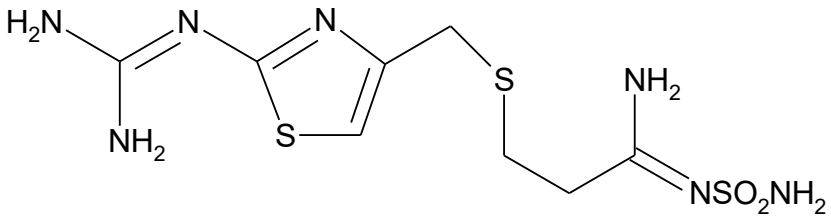
Chemical name:

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:



Physiochemical 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

CLINICAL TRIALS

Study demographics and trial design

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. Table 1 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 $p< 0.001$).

Study results

Table 1: 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 minutes	322	27.0	249	20.3	301	25.1	191	15.7
30 minutes	222	45.3	215	37.8	190	40.9	210	33.0
45 minutes	234	64.6	257	58.6	200	57.4	262	54.4
60 minutes	172	78.8	190	73.9	159	70.5	203	71.2
120 minutes	77	85.3	94	81.5	102	78.8	77	77.5
> 120 minutes	178	100.0	224	100.0	260	100.0	274	100.0

* Eps = episodes.

** Cumulative percentages are 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 2 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 2: 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 are based on the number episodes within each patient

FACT: famotidine antacid combination tablet
FCT: film-coated tablet
Antacid: calcium carbonate/magnesium hydroxide 21 mEq

DETAILED PHARMACOLOGY
I. HUMAN PHARMACOLOGY

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: 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 096 N=12, Fasted [Ref. C-3]	
	FACT	FCT	FACT	FCT	FACT	I.V.
$AUC_{0\text{-}24\ hr}$, ng•hr/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)	-	(0.86, 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, 1.02)	-	(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 ratio and 90% CI of $AUC_{0\text{-}24\ hr}$ (FACT/I.V.).
FCT=film-coated tablet.
I.V.=intravenous.

FACT: famotidine antacid combination tablet (famotidine 10 mg, calcium carbonate/ magnesium hydroxide 21 mEq)
FCT: famotidine 10 mg film-coated tablets

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.

Other Effects

Systemic pharmacologic effects of famotidine involving the CNS, cardiovascular, respiratory or endocrine systems have not been found to date. Serum prolactin levels do not rise after intravenous bolus doses of 20 mg of famotidine and no antiandrogenic effects have been detected.

II. ANIMAL PHARMACOLOGY

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%.

Mechanism of Action

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.

Absorption and Distribution

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. 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 and Excretion

The only metabolite of famotidine in rat and dog urine was the sulfoxide derivative, which was present in minor amounts. 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.

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*.

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.

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.

TOXICOLOGY

Acute Toxicity

Species	Sex	Route	LD_{50} (mg/kg)
Mouse	M	P.O.[x]	4,684
	F	P.O.[x]	3,233
Mouse	M	I.V. (4%)	254
	F	I.V. (4%)	358
Rat	M	P.O.[x]	4,907
	F	P.O.[x]	4,049
Rat	M	I.P.	987
	F	I.P.	814

[x]In solution (acidic, 50-55°C deionized water).

Subacute and Chronic Toxicity

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.

Reproduction Studies
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.

Mutagenicity
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.

Carcinogenicity
A 92-week oral carcinogenicity study was conducted in mice at 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.

Special Studies
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.

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PART III: CONSUMER INFORMATION

PEPCID® COMPLETE® Famotidine, Calcium Carbonate and Magnesium Hydroxide Tablets (Chewable)

This leaflet is part III of a three-part "Product Monograph" published when PEPCID® COMPLETE® was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about PEPCID® COMPLETE®. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:

PEPCID® COMPLETE® 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. PEPCID® COMPLETE® also prevents these symptoms brought on by consuming food and/or beverage.

What it does:

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.

When it should not be used:

Do not use Pepcid Complete

- if you are allergic to Famotidine or any nonmedicinal ingredients (see complete list) 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.

What the medicinal ingredient is:

Each tablet of PEPCID® COMPLETE® contains 10 mg of 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.

What the important nonmedicinal ingredients are:

PEPCID® COMPLETE® chewable tablets also contain the following 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 contain FD&C Blue #1 and D&C Yellow #10.

What dosage forms it comes in:

PEPCID® COMPLETE® is available as a chewable tablet.

WARNINGS AND PRECAUTIONS

This medicine may not be suitable for some people. BEFORE you use PEPCID® COMPLETE® talk to your doctor or pharmacist if:

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

Stop use and ask a doctor if:

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

INTERACTIONS WITH THIS MEDICATION

BEFORE you use PEPCID® COMPLETE® talk to your doctor or pharmacist if:

- You are taking a prescription drug, iron, calcium carbonate or zinc sulfate as some drug interactions could occur.
- You are using Itraconazole (for fungal infections).
- You are using antibiotics or drugs for HIV.

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

PROPER USE OF THIS MEDICATION

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

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.

Overdose:

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no

SIDE EFFECTS AND WHAT TO DO ABOUT THEM

PEPCID® COMPLETE® is generally well tolerated.

SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM

Symptoms / effects		Talk with your healthcare professional		Stop taking drug and get immediate medical help
		Only if severe	In all cases	
Very Rare	Dizziness, headache, sleepiness, weakness	√		
Very Rare	Stomach pain, diarrhea, dry mouth, nausea, vomiting		√	
Very Rare	Allergic reactions such as hives, rash, swelling, itching and difficulty to breath		√	

For any unexpected effects while taking PEPCID® COMPLETE® contact your doctor or pharmacist.

HOW TO STORE IT

- Store tablets at 15°C - 30°C. Protect from moisture.
- Keep this and all medicines out of the reach of children.

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/adverse-reaction-reporting.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.

MORE INFORMATION

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, McNeil Consumer Healthcare, division of Johnson and Johnson Inc., at:
1-800-4PEPCID

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

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