

PRODUCT MONOGRAPH

PEPTIC GUARD

(Famotidine Tablets, USP)

Tablets 10 mg

Histamine H₂ Receptor Antagonist

Mylan Pharmaceuticals ULC
85 Advance Road
Etobicoke, Ontario
M8Z 2S6

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(Famotidine Tablets, USP)

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THERAPEUTIC CLASSIFICATION

Histamine H₂ Receptor Antagonist

CLINICAL PHARMACOLOGY

PEPTIC GUARD (famotidine) is a competitive inhibitor of histamine H₂-receptors. The primary clinically important pharmacologic activity of PEPTIC GUARD is inhibition of gastric juice secretion. PEPTIC GUARD reduces the acid and pepsin content, as well as the volume, of basal, nocturnal, and stimulated gastric secretion.

INDICATIONS AND CLINICAL USE

PEPTIC GUARD (famotidine) is indicated in the treatment of the following conditions where a controlled reduction of gastric secretion is required, such as acid indigestion, heartburn, sour or upset stomach. PEPTIC GUARD (famotidine) is also indicated for the prevention of these symptoms when associated with the consumption of food and/or beverage including nocturnal symptoms associated with the evening meal and expected to cause sleep disturbance.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. Cross sensitivity in this class of compounds has been observed. Therefore, PEPTIC GUARD should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

PRECAUTIONS

General

In clinical trials, patients with other underlying acid gastrointestinal diseases (eg. 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 swallowing or if abdominal discomfort persists, the underlying cause should be determined. Symptomatic response to therapy with PEPTIC GUARD (famotidine) does not preclude the presence of gastric malignancy.

Patients with severe kidney disease, previous history of ulcer disease complications, severe coexisting illness, 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 PEPTIC GUARD (famotidine).

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 PEPTIC GUARD (famotidine).

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

Drug interactions

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, eg., 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.

Concomitant use of aluminum hydroxide/magnesium hydroxide at commonly used doses, does not influence the pharmacodynamics or bioavailability of famotidine. Famotidine does not affect gastric alcohol dehydrogenase and, consequently, blood ethanol levels.

Use in Obstetrics

Reproductive studies 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 prescription human dose (80 mg), 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.

Since the safe use of famotidine tablets in pregnant women has not been established, pregnant women should not use PEPTIC GUARD unless directed otherwise by a physician.

Nursing Mothers

Famotidine is detectable in human milk. Nursing mothers should either stop this drug or should stop nursing.

Pediatric Use

Safety and effectiveness in children have not been established. PEPTIC GUARD (famotidine) should not be administered to children under 12 years of age.

Use in Elderly Patients

No dosage adjustment is required based on age (see HUMAN PHARMACOLOGY, Pharmacokinetics).

ADVERSE REACTIONS

Famotidine has been demonstrated to be generally well tolerated. Adverse reactions reported in $\geq 1\%$ of patients were headache and dizziness. These occurred with comparable frequency in patients treated with placebo.

Laboratory parameters may be affected during treatment with famotidine, but the changes are usually not considered serious. Among the laboratory changes that were reported during clinical trials 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.

During marketed use of prescription doses, 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. Toxic epidermal necrolysis has been reported very rarely with H₂-receptor antagonists.

The following adverse reactions have been reported; however, a causal relationship to therapy with famotidine 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.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience to date with deliberate overdose. Doses of up to 800 mg/day 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.

The oral LD₅₀ of famotidine in male and female rats and mice was > 5000 mg/kg.

DOSAGE AND ADMINISTRATION

Adults and children 12 years of age or older: 10 mg, as required to relieve symptoms. For prevention of acid-related symptoms associated with the consumption of food and/or beverage: 10 mg 10 to 15 minutes before eating. Repeat if symptoms return, up to a maximum of 20 mg in a 24-hour period.

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

Concomitant Use with Antacids

Antacids may be given concomitantly if needed.

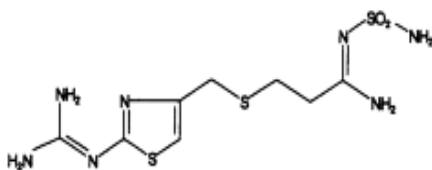
PHARMACEUTICAL INFORMATION

I. DRUG SUBSTANCE

Proper Name: Famotidine, USP

Chemical Name: Propanimidamide, *N'*-(aminosulfonyl)-3-[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio]-.

Structural formula:



Famotidine

Molecular formula: C₈H₁₅N₇O₂S₃

Molecular Weight: 337.45

Description: Famotidine is a white to pale yellowish-white crystalline powder that is freely soluble in glacial acetic acid; slightly soluble in methanol; very slightly soluble in water; and practically insoluble in ethanol. It has a melting point range of 163.0 - 164.5°C.

II. Composition: Each film coated tablet contains 10 mg of famotidine and the following non-medicinal ingredients:

microcrystalline cellulose; pregelatinized starch; talc, magnesium stearate; lactose, hydroxy propyl methylcellulose, titanium dioxide, triacetin, synthetic red iron oxide, and synthetic yellow iron oxide.

III. Stability and Storage Recommendations:

PEPTIC GUARD should be stored between 15° and 30° C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

PEPTIC GUARD (famotidine) 10 mg Tablets - Pink, film-coated, square, biconvex tablets, marked with "FM" over "10" on one side and plain on the other. Available in blister packs of 12 and 24 tablets.

INFORMATION FOR THE CONSUMER

PEPTIC GUARD ***FAMOTIDINE 10 MG TABLETS***

WHAT IS PEPTIC GUARD?

FOR WHAT CONDITIONS SHOULD IT-BE TAKEN?

PEPTIC GUARD tablets provide fast effective relief from heartburn and acid indigestion. In addition, when taken 10-15 minutes before a meal, PEPTIC GUARD can actually prevent heartburn before it starts.

Day or night, PEPTIC GUARD relieves and prevents heartburn. One tablet, taken before your evening meal can prevent nighttime heartburn symptoms so you can sleep through the night.

HOW DOES PEPTIC GUARD WORK?

Unlike antacids which neutralize existing stomach acid, but allow stomach acid to continue to be produced, PEPTIC GUARD→ actually reduces the production of excess stomach acid which can lead to heartburn pain. This enables PEPTIC GUARD→ to provide long lasting acid control, day or night.

FOR WHAT CONDITIONS SHOULD PEPTIC GUARD BE TAKEN?

PEPTIC GUARD offers fast and effective relief from heartburn, acid indigestion and upset or sour stomach due to excess stomach acid. PEPTIC GUARD also prevents these symptoms brought on by consuming food and/or beverage all day or all night.

HOW SHOULD PEPTIC GUARD BE TAKEN?

Adults and children 12 years of age or older: For relief of symptoms, take one (1) tablet. For prevention of acid-related symptoms brought on by consuming food and/or beverage, take one (1) tablet 10 to 15 minutes before eating. If symptoms return, you may take another tablet. Do not take more than two tablets during a 24-hour period. . If symptoms persist for more than two consecutive weeks, consult your physician.

WHEN SHOULD A PHYSICIAN OR PHARMACIST BE CONSULTED?

This medicine may not be suitable for some people. Consult with your physician or pharmacist before using if:

- You are allergic to any component of this product.
- You are pregnant or breast-feeding

- You have difficulty swallowing, or persistent abdominal discomfort (stomach pains).
- You have severe kidney disease or any other severe illnesses.
- You are over 40 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 NSAIDs 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.

PEPTIC GUARD is generally well tolerated. Should any unusual symptoms occur, a physician should be consulted.

WHAT ELSE CAN BE DONE TO HELP AVOID SYMPTOMS

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

DESCRIPTION

Each pink, square, round edged tablet is marked with “FM” over “10” on one side and plain on the other and is film-coated to ease swallowing.

INGREDIENTS

Active ingredient:

Each tablet of PEPTIC GUARD contains 10 mg of famotidine.

Non-medicinal ingredients:

Film-coated tablets contain the following non-medicinal ingredients: microcrystalline cellulose; pregelatinized starch; talc, magnesium stearate; lactose, hydroxy propyl methylcellulose, titanium dioxide, triacetin, synthetic red iron oxide, and synthetic yellow iron oxide.

HOW SHOULD PEPTIC GUARD BE STORED?

- Store these tablets at room temperature (15° to 30°C) and protect from light.
- It is advisable to keep blisters in carton until all tablets are used.
- Keep this and all medicines out of the reach of children.

Consult your physician or pharmacist if you need further information.

Product Monograph available on request to physicians and pharmacists.

Mylan Pharmaceuticals ULC
Toronto, Canada

PHARMACOLOGY

I. HUMAN PHARMACOLOGY

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. Famotidine was well-tolerated at these dose levels. Pharmacodynamic data from nighttime studies show that the activity of the 10 mg dose continues for up to 12 hours postdose.

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.

Pharmacokinetics

Famotidine is incompletely absorbed. The bioavailability of oral doses is 40-45%. Bioavailability may be slightly increased by food; however, this effect is of no clinical significance. Bioavailability of famotidine at recommended doses is not affected by customary doses of antacids. Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. C_{max} value of 41 ng/mL for the 10 mg film-coated tablet was 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. 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.

II. Animal Pharmacology

Famotidine inhibits gastric secretion evoked by histamine and other secretagogues. In dogs, the ED₅₀ 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, H₂-receptor antagonist. There was no effect *in vitro* on responses mediated by H₁-histamine, beta₁-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 H₂-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 H₂-receptor sites. However, in guinea pig atria, famotidine acted as a non-competitive H₂ 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.*	4,684
	F	P.O.*	3,233
Mouse	M	I.V. (4%)	254
	F	I.V. (4%)	358
Rat	M	P.O.*	4,907
	F	P.O.*	4,049
Rat	M	I.P.	987
	F	I.P.	814

* 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 embryoletality 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 embryoletality 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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