PRODUCT MONOGRAPH

[Pr]Ulcidine

Famotidine Tablets 20 mg; 40 mg, USP

HISTAMINE H_2 RECEPTOR ANTAGONIST

Valeant Canada limitée/Limited
4787 Levy Street
Montreal, Quebec
H4R 2P9

Date of Preparation:
May 6, 2005

Control #: 098469

PRODUCT MONOGRAPH

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Famotidine tablets 20 mg; 40 mg, USP

Histamine H_2 Receptor Antagonist

CLINICAL PHARMACOLOGY

Ulcidine (famotidine) is a competitive inhibitor of histamine H_2-receptors. The primary clinically important pharmacologic activity of Ulcidine is inhibition of gastric juice secretion. Ulcidine reduces the acid and pepsin content, as well as the volume, of basal, nocturnal, and stimulated gastric secretion.

PHARMACOKINETICS

Absorption: rapid, incomplete, oral bioavailability: 40-45 %	
Protein binding: low (15-20 %)	
Biotransformation: hepatic, minimal first pass metabolism	
Elimination half-life: with normal renal function 2.5-3.5 hrs with reduced creatinine clearance 10: 20 or more < hrs	
Mean serum concentration resulting in 50 % inhibition of pentagastrin-stimulated acid secretion: 13 ng/mL	
Tmax:	1 to 3 hrs
Time to peak effect:	1 to 3 hrs
Onset of action:	1 hr

Duration of action: (nocturnal and basal)	10 to 12 hrs
Elimination:	primarily renal (65-70%) metabolic (30-35%)
Renal Clearance:	250-450 mL/min
Distribution:	breast milk and cerebral spinal fluid

A comparative bioavailability study, of ICN Canada Ulcidine and Merck Sharp & Dohme (Pepcid) 40 mg tablets showed the following results.

SUMMARY TABLE OF THE COMPARATIVE BIOAVAILABILITY DATA

Ulcidine

(40 mg)

From measured data

Geometric Mean

Arithmetic Mean (CV%)

Parameter	**Test**	**Reference**	**Ratio of Geometric Means (%)**
	Ulcidine	**Pepcid**	
	ICN Canada	**MSD Canada**	
AUC_T	**704.43**	**696.43**	**101**
(ng.hr/mL)	**722.22(22.7)**	**722.79(27.6)**	
AUC_I	**745.95**	**747.62**	**100**
(ng.hr/mL)	**764.62(22.7)**	**772.85(25.9)**	
C_{max}	**117.05**	**118.97**	**98**
(ng/mL)	**120.68(25.68)**	**124.54(30.45)**	
$T_{max(h)}$	**2.5**	**2.5**	
$T_{1/2}$(h)	**3.5**	**3.5**	

The T_{max} and $T_{1/2}$ parameters are expressed as the arithmetic means

INDICATIONS AND CLINICAL USE

Ulcidine (famotidine) is indicated in the treatment of the following conditions where a controlled reduction of gastric secretion is required:

1. Treatment of acute duodenal ulcer;
2. Prophylactic use in duodenal ulcer;
3. Treatment of acute benign gastric ulcer;
4. Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome);
5. Treatment of gastroesophageal reflux disease (GERD).
6. Maintenance of remission of patients with GERD.

CONTRAINDICATIONS

Ulcidine (famotidine) is contraindicated in patients with known hypersensitivity to the drug or any ingredient of the formulation.

WARNINGS AND PRECAUTIONS

Patients with Severe Renal Insufficiency

Dosing intervals may need to be prolonged in patients with advanced renal insufficiency (creatinine clearance <10 mL/min) to adjust for the longer elimination half-life of famotidine. (SEE CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

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, 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. In addition, studies with famotidine have shown no augmentation of expected blood alcohol levels resulting from alcohol ingestion.

Use in Gastric Ulcer

Gastric malignancy should be excluded prior to initiation of therapy of gastric ulcer with Ulcidine. Symptomatic response of gastric ulcer to therapy with Ulcidine does not preclude the presence of gastric malignancy.

Use in Pregnancy

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 human dose, 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 Ulcidine in pregnant women has not been established, the benefits of treatment with Ulcidine should be weighed against potential risks.

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.

Use in Elderly Patients

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

Pharmacokinetics).

ADVERSE REACTIONS

Ulcidine (famotidine) is usually well tolerated; most adverse reactions have been mild and transient. The adverse reactions listed below have been reported during clinical trials in 2333 patients. In those controlled clinical trials in which famotidine was compared to placebo, the overall incidence of adverse experiences in the group which received famotidine 40 mg at bedtime, was similar to the placebo group. No antiandrogenic or other adverse hormonal effects have been observed.

The following adverse reactions have been reported at a rate of greater than 1% in patients on therapy with famotidine in controlled clinical trials, and may be causally related to the drug: headache (4.6%), dizziness (1.2%), constipation (1.2%) and diarrhea (1.6%).

Other reactions have been reported in clinical trials but occurred under circumstances where a causal relationship could not be established. However, in these rarely reported events, that possibility cannot be excluded. Therefore, these observations are listed to serve as alerting information to physicians.

Gastrointestinal	**8.0%**	
Nausea	1.6%	
Vomiting	0.9%	
Anorexia	0.5%	
Abdominal discomfort	0.3%	
Dry mouth	0.2%	
Nervous System/Psychiatric	**7.3%**	
Insomnia	0.6%	
Somnolence	0.4%	
Anxiety	0.3%	
Paresthesia	0.3%	
Depression	0.2%	
Libido decreased	0.1%	
Respiratory	**4.4%**	
Bronchospasm	<0.1%	
Body as a Whole	**3.0%**	
Fatigue		0.6%
Asthenia	0.3%	
Fever	0.2%	
Musculoskeletal	**1.7%**	
Musculoskeletal pain	0.1%	
Arthralgia	0.1%	
Skin	**1.7%**	
Pruritus	0.4%	
Rash	0.3%	
Alopecia	0.2%	
Flushing	0.2%	
Acne	0.1%	
Dry skin	0.1%	
Cardiovascular	**1.0%**	
Palpitations	0.2%	
Special Senses	**0.9%**	
Taste disorder	0.1%	
Tinnitus	0.1%	
Orbital Edema	< 0.1%	
Urogenital	**0.9%**	

The following additional adverse reactions have been reported since famotidine was marketed: urticaria, liver enzymes abnormalities, cholestatic jaundice, anaphylaxis, angioedema. 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 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.

Laboratory Abnormalities

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, BUN, and serum creatinine. These changes were rarely of clinical significance.

Only three patients had to be discontinued from therapy because of laboratory adverse experiences, however laboratory abnormalities were present at baseline.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience to date with deliberate overdosage. 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 LD_{50} of famotidine in male and female rats and mice was >5000 mg/kg.

DOSAGE AND ADMINISTRATION

DUODENAL ULCER

Acute Therapy

The recommended adult oral dosage of Ulcidine (famotidine) for acute duodenal ulcer is 40 mg once a day at bedtime. Treatment should be given for 4 to 8 weeks, but the duration of treatment may be shortened if healing can be documented. Healing occurs within 4 weeks in most cases of duodenal ulcer.

Maintenance Therapy

For the prevention of recurrence of duodenal ulcer, it is recommended that therapy with Ulcidine be continued with a dose of 20 mg once a day at bedtime, for a duration of up to 6 to 12 months depending on the severity of the condition.

BENIGN GASTRIC ULCER

Acute Therapy

The recommended adult oral dosage for acute benign gastric ulcer is 40 mg once a day at bedtime. Treatment should be given for 4 to 8 weeks, but the duration of treatment may be shortened if healing can be documented.

PATHOLOGICAL HYPERSECRETORY CONDITIONS (SUCH AS ZOLLINGER-ELLISON SYNDROME)

The dosage of Ulcidine in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult oral starting dose for pathological hypersecretory conditions is 20 mg q6h. In some patients, a higher starting dose may be required. Doses should be adjusted to individual patient needs and should continue as long as clinically indicated. Doses up to 800 mg/day have been administered to some patients with severe Zollinger-Ellison syndrome.

GASTROESOPHAGEAL REFLUX DISEASE

The recommended dosage for the symptomatic relief of gastroesophageal reflux disease is 20 mg of Ulcidine (famotidine) twice a day.

For the treatment of esophageal erosion or ulceration associated with gastroesophageal reflux disease, the recommended dosage is 40 mg of famotidine twice a day.

For the maintenance of remission of patients with GERD, the recommended dosage is 20 mg of famotidine twice a day.

Concomitant Use with Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Severe Renal Insufficiency

In patients with advanced renal insufficiency, i.e., with a creatinine clearance less than 10 mL/min., the elimination half-life of Ulcidine may exceed 20 hours reaching approximately 24 hours in anuric patients.

To avoid excess accumulation of the drug, the dosing interval of Ulcidine may be prolonged to 36-48 hours as indicated by the patient's clinical response.

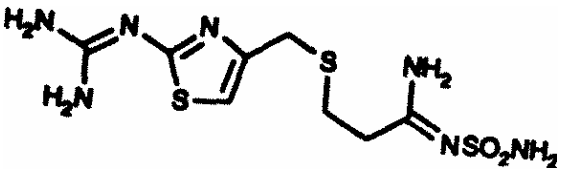
PHARMACEUTICAL INFORMATION

Drug Substance: Famotidine USP

Chemical Name : (1) Propanimidamide,N'-(amino-sulfonyl)-3-[[[2-[(diamino-methylene)amino]-4-thiazolyl]methyl]thio]

(2) [1-Amino-3-[[[2-[(diamino-methylene)amino]-4-thiazolyl] methyl]thio]propylidene]sulfamide

Structural Formula:



Molecular Formula: $C_8H_{15}N_70_2S_3$

Molecular Weight : 337.44

Description: famotidine occurs as a white to pale yellow, odorless, crystalline powder that is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water and practically insoluble in ethanol.

Composition:

Ulcidine (famotidine) tablets contain:

Medicinal Ingredient

- famotidine,USP

Non-medicinal Ingredients

- microcrystalline cellulose
- lactose
- magnesium stearate
- pregelatinized starch
- talc

Film-coating Materials:

- Opaspray Tan K-1-17002 for Ulcidine 20 mg

- alcohol SDA 3A

- titanium dioxide
- hydroxypropyl cellulose
- synthetic yellow iron oxide
- synthetic red iron oxide

• Opaspray Orange K-1-13000 for Ulcidine 40 mg

- alcohol SDA 3A
- titanium dioxide
- hydroxypropyl cellulose
- synthetic yellow iron oxide
- synthetic red iron oxide

• Carnauba wax NF

Film Coating Base Solution

- Alcohol (SDAG-1G)
- Povidone USP
- Methylene chloride
- Acetylated monoglycerides
- Hydroxy methyl propyl cellulose

Storage Recommendations: **ULCIDINE** tablets should be stored in well-closed, light-resistant containers at controlled room temperature (15-30^{o} C).

Protect from humidity.

AVAILABILITY

Each flesh-colored, film-coated, round tablet, embossed ICN on one side and U11 on the other side contains 20 mg of famotidine, USP. Bottles of 100's; 500's.

Each light brown-colored, film-coated, round tablet, embossed ICN on one side and U12 on the other side contains 40 mg of famotidine, USP. Bottles of 100's; 500's.

INFORMATION TO THE CONSUMER

Histamine H_2-receptor antagonists, also known as H_2-blockers, are used to treat duodenal ulcers and prevent their return. They are also used to treat gastric ulcers and in some conditions, such as Zollinger-Ellison disease, in which the stomach produces too much acid. H_2-blockers may also be used for other conditions as determined by your doctor.

H_2-blockers work by decreasing the amount of acid produced by the stomach.

It is very important that you read and understand the following information. If any of it causes you special concern, check with your doctor. Also, if you have any questions or if you want more information about this medicine or your medical problem, ask your doctor, or pharmacist.

Before Using Ulcidine:

* tell your doctor if you have ever had any unusual or allergic reaction to famotidine.
* H_2-blockers have not been studied in pregnant women. In animal studies, famotidine has not been shown to cause birth defects or other problems. Make sure your doctor knows ifyou are pregnant or if you may become pregnant before taking H2-blockers.
* famotidine passes into the breast milk and may cause unwanted effects, such as decreased amount of stomach acid and increased excitement, in the nursing baby. It may be necessary for you to take another medicine or to stop breast-feeding during treatment. Be sure you have discussed the risks and benefits of the medicine with your doctor.
* the safety of famotidine in children has not been established.
* confusion and dizziness may be especially likely to occur in elderly patients, who are usually more sensitive than younger adults to the effects of H_2-blockers.
* When you are taking or receiving H_2-blockers it is especially important that your doctor or pharmacist know if you are taking any other prescription or nonprescription medication:
    - o aminophylline (e.g., Phyllocontin)
    - o anticoagulants (blood thinners)

o caffeine containing drugs

o metoprolol (e.g., Lopresor)

o oxtriphylline (e.g., Choledyl)

o phenytoin (e.g., Dilantin)

o propanolol (e.g., Inderal)

o theophylline (e.g., Somophyllin)

o tricyclic antidepressants

o ketoconazole; H_2-blockers may decrease the effects of ketoconazole; H_2-blockers should be taken at least 2 hours after ketoconazole.

The presence of other medical problems may affect the use of H_2-blockers. Make sure you tell your doctor if you have any other medical problem, especially **kidney or liver disease**.

Proper Use of Ulcidine:

Take this medicine for the full time of treatment, even if you begin to feel better.

If you miss a dose of this medicine, take it as soon as possible. However, if it is almost time for your next dose, skip the missed dose and go back to your regular dosing schedule. Do **NOT DOUBLE** doses.

Storage: * keep out of the reach of children

* store away from heat and direct light

* do not store the tablets in the bathroom, near the kitchen sink, or in other damp places. Heat or moisture may cause the medicine to break down.

Some tests may be affected by H_2-blockers. Tell the doctor in charge that you are taking Ulcidine (famotidine) before:

* you have any skin tests for allergies

* you have any tests to determine how much acid your stomach produces
* Avoid use of foods, drinks, or other medications that may cause gastrointestinal irritation.
* Discontinue smoking or at least avoid smoking after the last dose of the day.
* Avoid alcoholic beverages.
* Check with your doctor if condition does not improve or worsens.

Side Effects of H_2-blockers:

Along with its needed effects, a medicine may cause some unwanted effects. Although not all of these side effects may occur, if they do occur check with your doctor:

* headache
* constipation
* diarrhea
* skin rash, burning, itching, redness
* confusion
* fast, pounding, or irregular heartbeat; or slow heartbeat
* fever
* sore throat and fever
* swelling
* tightness in chest
* unusual bleeding or bruising
* unusual tiredness or weakness

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, the onset of the antisecretory effect occurred within one hour; the maximum effect was dose-dependent, occurring within one to three hours. Duration of inhibition of secretion was 10 to 12 hours. Single oral doses of 20 and 40 mg inhibited basal nocturnal acid secretion in all subjects; mean gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. Similar doses given in the morning suppressed food-stimulated acid secretion in all subjects, with mean suppression of 76% and 84%,

respectively, 3 to 5 hours after drug, and of 25% and 30%, respectively, 8 to 10 hours after drug; however, in some subjects who received the 20 mg dose, the antisecretory effect was dissipated earlier, within 6 to 8 hours. There was no cumulative effect with repeated doses. The basal nocturnal intragastric pH was raised by evening doses of 20 and 40 mg of famotidine to mean values of 5.0 and 6.4, respectively. When famotidine was given in the morning, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5.0.

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.

The presence of gastroeophageal reflux disease appears to correlate best with the percentage of time over 24 hours during which the esophagus is exposed to acid. In gastroesophageal reflux disease patients, 20 mg twice a day and 40 mg twice a day of famotidine reduced intraesophageal acid exposure into the normal range as measured by 24 hour intraesophageal pH monitoring. In clinical studies of gastroesophageal reflux disease patients with esophagitis, 40 mg twice a day was more effective than 20 mg twice a day in healing esophageal lesions. Both dosage regimens were superior to placebo.

In patients treated for six months with famotidine, relapse of esophageal erosion or ulceration was significantly less than in patients treated with placebo. Famotitine was also shown to be superior to placebo in preventing symptomatic deterioration.

Other Effects

Systematic pharmacologic effects of famotidine in 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, or slightly decreased by antacids; however, these effects are of no clinical consequence. Famotidine undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1 to 3 hours. 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 to 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 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., famotidine elimination half-life may exceed 20 hours and adjustment of dosing intervals may be necessary (see PRECAUTIONS, 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 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 was 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 Toxicology

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^{o}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.

Reproductive 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 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 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/8mL/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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