FRESENIUS KABI

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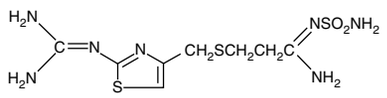
FAMOTIDINE
INJECTION, USP

Rx only

DESCRIPTION:
The active ingredient in famotidine injection is a histamine H_2–receptor antagonist. [1-Amino-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]-methyl]thio]propylidene] sulfamide. Its structural formula is:



$C_8H_{15}N_7O_2S_3$ M.W. 337.45

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.

Famotidine Injection, USP is supplied as a sterile concentrated solution for intravenous injection only. Each mL of the solution contains 10 mg of famotidine and the following inactive ingredients: L-aspartic acid 4 mg, mannitol 20 mg, Water for Injection q.s. 1 mL.

CLINICAL PHARMACOLOGY IN ADULTS:
GI Effects
Famotidine is a competitive inhibitor of histamine H_2–receptors. The primary clinically important pharmacologic activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by famotidine, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, famotidine inhibited basal and nocturnal gastric secretion, as well as secretion stimulated by food and pentagastrin. 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 by doses of 20 and 40 mg was 10 to 12 hours.

After intravenous administration, the maximum effect was achieved within 30 minutes. Single intravenous doses of 10 and 20 mg inhibited nocturnal secretion for a period of 10 to 12 hours. The 20 mg dose was associated with the longest duration of action in most subjects.

Single evening oral doses of 20 and 40 mg inhibited basal and nocturnal acid secretion in all subjects; mean nocturnal gastric acid secretion was inhibited by 86% and 94%, respectively, for a period of at least 10 hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84%, respectively, 3 to 5 hours after administration, and 25% and 30%, respectively, 8 to 10 hours after administration. In some subjects who received the 20 mg dose, however, the antisecretory effect was dissipated within 6 to 8 hours. There was no cumulative effect with repeated doses. The 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 after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5.

Famotidine had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by famotidine.

Other Effects
Systemic effects of famotidine in the CNS, cardiovascular, respiratory or endocrine systems were not noted in clinical pharmacology studies. Also, no antiandrogenic effects were noted (see **ADVERSE REACTIONS**). Serum hormone levels, including prolactin, cortisol, thyroxine (T_4), and testosterone, were not altered after treatment with famotidine.

Pharmacokinetics
Orally administered famotidine is incompletely absorbed and its bioavailability is 40 to 45%. 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 to 70%) and metabolic (30 to 35%) routes. Renal clearance is 250 to 450 mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65 to 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, the elimination half-life of famotidine may exceed 20 hours and adjustment of dose or dosing intervals in moderate and severe renal insufficiency may be necessary (see **PRECAUTIONS, DOSAGE AND ADMINISTRATION**).

In elderly patients, there are no clinically significant age-related changes in the pharmacokinetics of famotidine. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (see **PRECAUTIONS, *Geriatric Use***).

Clinical Studies
The majority of clinical study experience involved oral administration of famotidine tablets, and is provided herein for reference.

Duodenal Ulcer
In a U.S. multicenter, double-blind study in outpatients with endoscopically confirmed duodenal ulcer, orally administered famotidine was compared to placebo. As shown in Table 1, 70% of patients treated with famotidine 40 mg h.s. were healed by week 4.

Table 1
Outpatients with Endoscopically Confirmed Healed Duodenal Ulcers

	Famotidine 40 mg h.s. (N=89)	Famotidine 20 mg b.i.d. (N=84)	Placebo h.s. (N=97)
Week 2	**32%	**38%	17%
Week 4	**70%	**67%	31%

**Statistically significantly different than placebo ($p<0.001$)

Patients not healed by week 4 were continued in the study. By week 8, 83% of patients treated with famotidine had healed versus 45% of patients treated with placebo. The incidence of ulcer healing with famotidine was significantly higher than with placebo at each time point based on proportion of endoscopically confirmed healed ulcers.

In this study, time to relief of daytime and nocturnal pain was significantly shorter for patients receiving famotidine than for patients receiving placebo; patients receiving famotidine also took less antacid than the patients receiving placebo.

Long-Term Maintenance
Treatment of Duodenal Ulcers
Famotidine, 20 mg p.o. h.s. was compared to placebo h.s. as maintenance therapy in two double-blind, multicenter studies of patients with endoscopically confirmed healed duodenal ulcers. In the U.S. study the observed ulcer incidence within 12 months in patients treated with placebo was 2.4 times greater than in the patients treated with famotidine. The 89 patients treated with famotidine had a cumulative observed ulcer incidence of 23.4% compared to an observed ulcer incidence of 56.6% in the 89 patients receiving placebo ($p<0.01$). These results were confirmed in an international study where the cumulative observed ulcer incidence within 12 months in the 307 patients treated with famotidine was 35.7%, compared to an incidence of 75.5% in the 325 patients treated with placebo ($p<0.01$).

Gastric Ulcer
In both a U.S. and an international multicenter, double-blind study in patients with endoscopically confirmed active benign gastric ulcer, orally administered famotidine, 40 mg h.s., was compared to placebo h.s. Antacids were permitted during the studies, but consumption was not significantly different between the famotidine and placebo groups. As shown in Table 2, the incidence of ulcer healing (dropouts counted as unhealed) with famotidine was statistically significantly better than placebo at weeks 6 and 8 in the U.S. study, and at weeks 4, 6 and 8 in the international study, based on the number of ulcers that healed, confirmed by endoscopy.

Table 2
Patients with Endoscopically Confirmed Healed Gastric Ulcers

	U.S. Study		International Study	
	Famotidine 40 mg h.s. (N=74)	Placebo h.s. (N=75)	Famotidine 40 mg h.s. (N=149)	Placebo h.s. (N=145)
Week 4	45%	39%	† 47%	31%
Week 6	† 66%	44%	† 65%	46%
Week 8	***78%	64%	† 80%	54%

***,† Statistically significantly better than placebo ($p\leq0.05$, $p\leq0.01$ respectively)

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving famotidine than for patients receiving placebo; however, in neither study was there a statistically significant difference in the proportion of patients whose pain was relieved by the end of the study (week 8).

Gastroesophageal Reflux Disease (GERD)
Orally administered famotidine was compared to placebo in a U.S. study that enrolled patients with symptoms of GERD and without endoscopic evidence of erosion or ulceration of the esophagus. Famotidine 20 mg b.i.d. was statistically significantly superior to 40 mg h.s. and to placebo in providing a successful symptomatic outcome, defined as moderate or excellent improvement of symptoms (Table 3).

Table 3
% Successful Symptomatic Outcome

	Famotidine 20 mg b.i.d. (N=154)	Famotidine 40 mg h.s. (N=149)	Placebo (N=73)
Week 6	82††	69	62

†† $p\leq0.01$ vs Placebo

By two weeks of treatment, symptomatic success was observed in a greater percentage of patients taking famotidine 20 mg b.i.d. compared to placebo ($p\leq0.01$).

Symptomatic improvement and healing of endoscopically verified erosion and ulceration were studied in two additional trials. Healing was defined as complete resolution of all erosions or ulcerations visible with endoscopy. The U.S. study comparing famotidine 40 mg p.o. b.i.d. to placebo and famotidine 20 mg p.o. b.i.d., showed a significantly greater percentage of healing for famotidine 40 mg b.i.d. at weeks 6 and 12 (Table 4).

Table 4
% Endoscopic Healing – U.S. Study

	Famotidine 40 mg b.i.d. (N=127)	Famotidine 20 mg b.i.d. (N=125)	Placebo (N=66)
Week 6	48†††, ‡‡	32	18
Week 12	69†††, ‡	54†††	29

††† $p\leq0.01$ vs Placebo
‡ $p\leq0.05$ vs Famotidine 20 mg b.i.d.
‡‡ $p\leq0.01$ vs Famotidine 20 mg b.i.d.

As compared to placebo, patients who received famotidine had faster relief of daytime and nighttime heartburn and a greater percentage of patients experienced complete relief of nighttime heartburn. These differences were statistically significant.

In the international study, when famotidine 40 mg p.o. b.i.d. was compared to ranitidine 150 mg p.o. b.i.d., a statistically significantly greater percentage of healing was observed with famotidine 40 mg b.i.d. at week 12 (Table 5). There was, however, no significant difference among treatments in symptom relief.

Table 5
% Endoscopic Healing - International Study

	Famotidine 40 mg b.i.d. (N=175)	Famotidine 20 mg b.i.d. (N=93)	Ranitidine 150 mg b.i.d. (N=172)
Week 6	48	52	42
Week 12	71‡‡‡	68	60

‡‡‡ $p\leq0.05$ vs Ranitidine 150 mg b.i.d.

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)
In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome with or without multiple endocrine adenomas, famotidine significantly inhibited gastric acid secretion and controlled associated symptoms. Orally administered doses from 20 to 160 mg q 6 h maintained basal acid secretion below 10 mEq/hr; initial doses were titrated to the individual patient need and subsequent adjustments were necessary with time in some patients. Famotidine was well tolerated at these high dose levels for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of gynecomastia, increased prolactin levels, or impotence which were considered to be due to the drug.

CLINICAL PHARMACOLOGY IN PEDIATRIC PATIENTS:
Pharmacokinetics
Table 6 presents pharmacokinetic data from published studies of small numbers of pediatric patients given famotidine intravenously. Areas under the curve (AUCs) are normalized to a dose of 0.5 mg/kg IV for pediatric patients and compared with an extrapolated 40 mg intravenous dose in adults (extrapolation based on results obtained with a 20 mg IV adult dose).

Table 6
Pharmacokinetic Parameters[a] of Intravenous Famotidine

Age (N=number of patients)	Area under the Curve (AUC) (ng-hr/mL)	Total Clearance (Cl) (L/hr/kg)	Volume of Distribution (V_d) (L/kg)	Elimination Half-life ($T_{1/2}$) (hours)
1-11 yrs (N=20)	1089 ± 834	0.54 ± 0.34	2.07 ± 1.49	3.38 ± 2.60
11-15 yrs (N=6)	1140 ± 320	0.48 ± 0.14	1.5 ± 0.4	2.3 ± 0.4
Adult (N=16)	1726[b]	0.39 ± 0.14	1.3 ± 0.2	2.83 ± 0.99

[a]Values are presented as means ± SD unless indicated otherwise.
[b]Mean value only.

Values of pharmacokinetic parameters for pediatric patients, ages 1 to 15 years, are comparable to those obtained for adults.

Bioavailability studies of 8 pediatric patients (11 to 15 years of age) showed a mean oral bioavailability of 0.5 compared to adult values of 0.42 to 0.49. Oral doses of 0.5 mg/kg achieved an AUC of 580 ± 60 ng-hr/mL in pediatric patients 11 to 15 years of age compared to 482 ± 181 ng-hr/mL in adults treated with 40 mg orally.

Pharmacodynamics
Pharmacodynamics of famotidine were evaluated in 5 pediatric patients 2 to 13 years of age using the sigmoid E_{max} model. These data suggest that the relationship between serum concentration of famotidine and gastric acid suppression is similar to that observed in one study of adults (Table 7).

Table 7
Pharmacodynamics of famotidine using the sigmoid E_{max} model

	EC_{50} (ng/mL)*
Pediatric Patients	26 ± 13
Data from one study	
a) healthy adult subjects	26.5 ± 10.3
b) adult patients with upper GI bleeding	18.7 ± 10.8

*Serum concentration of famotidine associated with 50% maximum gastric acid reduction. Values are presented as means ± SD.

Four published studies (Table 8) examined the effect of famotidine on gastric pH and duration of acid suppression in pediatric patients. While each study had a different design, acid suppression data over time are summarized as follows:

Table 8

Dosage	Route	Effect[a]	Number of Patients
0.3 mg/kg, single dose	IV	gastric pH >3.5 for 8.7 ± 4.7[b] hours	6
0.4-0.8 mg/kg	IV	gastric pH >4 for 6-9 hours	18
0.5 mg/kg, single dose	IV	a >2 pH unit increase above baseline in gastric pH for >8 hours	9
0.5 mg/kg b.i.d.	IV	gastric pH >5 for 13.5 ± 1.8[b] hours	4
0.5 mg/kg b.i.d.	oral	gastric pH >5 for 5.0 ± 1.1[b] hours	4

[a]Values reported in published literature.
[b]Means ± SD.

INDICATIONS AND USAGE:
Famotidine injection, supplied as a concentrated solution for intravenous injection, is intended for intravenous use only. Famotidine injection is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage forms for short term use in patients who are unable to take oral medication for the following conditions:

1. *Short term treatment of active duodenal ulcer.* Most adult patients heal within 4 weeks; there is rarely reason to use famotidine at full dosage for longer than 6 to 8 weeks. Studies have not assessed the safety of famotidine in uncomplicated active duodenal ulcer for periods of more than 8 weeks.

2. *Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.* Controlled studies in adults have not extended beyond one year.

3. *Short term treatment of active benign gastric ulcer.* Most adult patients heal within 6 weeks. Studies have not assessed the safety or efficacy of famotidine in uncomplicated active benign gastric ulcer for periods of more than 8 weeks.

4. *Short term treatment of gastroesophageal reflux disease (GERD).* Famotidine is indicated for short term treatment of patients with symptoms of GERD (see **CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies***).

Famotidine is also indicated for the short term treatment of esophagitis due to GERD including erosive or ulcerative disease diagnosed by endoscopy (see **CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies***).

5. *Treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison Syndrome, multiple endocrine adenomas)* (see **CLINICAL PHARMACOLOGY IN ADULTS, *Clinical Studies***).

CONTRAINDICATIONS:
Hypersensitivity to any component of this product. Cross sensitivity in this class of compounds has been observed. Therefore, famotidine should not be administered to patients with a history of hypersensitivity to other H_2 -receptor antagonists.

PRECAUTIONS:
General
Symptomatic response to therapy with famotidine injection does not preclude the presence of gastric malignancy.

Patients with Moderate or Severe Renal Insufficiency
Since CNS adverse effects have been reported in patients with moderate and severe renal insufficiency, longer intervals between doses or lower doses may need to be used in patients with moderate (creatinine clearance <50 mL/min) or severe (creatinine clearance <10 mL/min) renal insufficiency to adjust for the longer elimination half-life of famotidine (see **CLINICAL PHARMACOLOGY IN ADULTS, DOSAGE AND ADMINISTRATION**).

Drug Interactions
No drug interactions have been identified. 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 include warfarin, theophylline, phenytoin, diazepam, aminopyrine and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

Carcinogenesis, Mutagenesis, Impairment of Fertility
In a 106 week study in rats and a 92 week study in mice given oral doses of up to 2,000 mg/kg/day (approximately 2,500 times the recommended human dose for active duodenal ulcer), there was no evidence of carcinogenic potential for famotidine.

Famotidine was negative in the microbial mutagen test (Ames test) using *Salmonella typhimurium* and *Escherichia coli* with or without rat liver enzyme activation at concentrations up to 10,000 mcg/plate. In *in vivo* studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

In studies with rats given oral doses of up to 2,000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

Pregnancy
Pregnancy Category B
Reproductive studies have been performed in rats and rabbits at oral doses of up to 2,000 and 500 mg/kg/day, respectively, and in both species at IV doses of up to 200 mg/kg/day, and have revealed no significant evidence of impaired fertility or harm to the fetus due to famotidine. While no direct fetotoxic effects have been observed, sporadic abortions occurring only in mothers displaying marked decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day (250 times the usual human dose) or higher. There are, however, no adequate or well-controlled studies in pregnant women. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Studies performed in lactating rats have shown that famotidine is secreted into breast milk. Transient growth depression was observed in young rats suckling from mothers treated with maternotoxic doses of at least 600 times the usual human dose. Famotidine is detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from famotidine, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use
Use of famotidine in pediatric patients 1 to 16 years of age is supported by evidence from