DESCRIPTION:
The active ingredient in famotidine injection is a histamine H₂-receptor antagonist. (1-Amino-3-[2-[(diaminomethylene)amino]-4-phenyl-2-(4-methyl-[thio]propylidene) sulfamide. Its structural formula is:

\[
\text{C}_8\text{H}_{15}\text{N}_7\text{O}_2\text{S}_3 \quad \text{M.W. 337.45}
\]

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 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 H₂ 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 hyposecretors, 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 antisecretionary effect occurred 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 and 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 excocrine 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 antianadrogenic effects were noted. (See ADVERSE REACTIONS.) Serum hormone levels, including prolactin, cortisol, thyroxine (T₄), 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 be prolonged by 65% with 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 | Famotidine | Placebo |
| 40 mg h.s. | 20 mg b.i.d. | h.s. |
| (N=89) | (N=84) | (N=97) |
| Week 2 **33% | **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 a 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. Patients treated with famotidine had a cumulative 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 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 |
|------------------|------------------|------------------|
| Famotidine Placebo | Famotidine Placebo |
| 40 mg h.s. | 20 mg h.s. | h.s. |
| (N=74) | (N=75) | (N=149) |
| Week 4 | 45% | 15% |
| Week 6 | 61% | 44% |
| Week 8 | 82% | 54% |

*** Statistically significantly better than placebo (p<0.01) respectively

Time to complete relief of daytime and nighttime pain was statistically significantly shorter for patients receiving famotidine than for patients
Gastroesophageal Reflux Disease (GERD). Orally administered famotidine was compared to placebo in a U.S. study that permitted 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, as defined as moderate or excellent improvement of symptoms (Table 3).

<table>
<thead>
<tr>
<th>Week 6</th>
<th>p&lt;0.01 vs Placebo</th>
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<tbody>
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</table>

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<0.01).

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 ranitidine 150 mg 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>
<thead>
<tr>
<th>Table 4</th>
<th>% Endoscopic Healing - U.S. Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine 40 mg b.i.d.</td>
<td>Placebo</td>
</tr>
<tr>
<td>(N=127)</td>
<td>(N=125)</td>
</tr>
<tr>
<td>Week 6</td>
<td>48±10</td>
</tr>
<tr>
<td>Week 12</td>
<td>62±11</td>
</tr>
<tr>
<td>* p&lt;0.01 vs Placebo</td>
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</tbody>
</table>

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>
<thead>
<tr>
<th>Table 5</th>
<th>% Endoscopic Healing - International Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Famotidine 40 mg b.i.d.</td>
<td>Ranitidine 150 mg b.i.d.</td>
</tr>
<tr>
<td>(N=175)</td>
<td>(N=93)</td>
</tr>
<tr>
<td>Week 6</td>
<td>48±10</td>
</tr>
<tr>
<td>Week 12</td>
<td>63±11</td>
</tr>
<tr>
<td>* p&lt;0.05 vs Ranitidine 150 mg b.i.d.</td>
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</tbody>
</table>

Pathological Hypersecretory Conditions (e.g., Zollinger-Ellison Syndrome, Multiple Endocrine Adenomas)

In studies of patients with pathological hypersecretory conditions such as Zollinger-Ellison Syndrome, a pathological condition of patients with multiple endocrine adenomas, famotidine significantly inhibited gastric acid secretion and controlled associated symptoms. Orally administered doses of famotidine 20 mg b.i.d. to 160 mg q.6h 6 h maintained basal acid secretion below 10 mEq/h; initial doses were titrated to the dosage that the patient need and subsequent adjustments were necessary with time in some patients. Famotidine was well tolerated at these high doses for prolonged periods (greater than 12 months) in eight patients, and there were no cases reported of pyloric stenosis, increased pyloric muscle tone, or impotence which were considered to be due to the drug.

**Clinical Pharmacology in Pediatric Patients:**

Table 6 presents pharmacokinetic data from published studies of small numbers of pediatric patients. Famotidine given intravenously and orally, is 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>
<thead>
<tr>
<th>Table 6</th>
<th>Pharmacokinetic Parameters of Intravenous Famotidine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>(N=number of patients)</td>
</tr>
<tr>
<td>1-11 yrs</td>
<td>(N=20)</td>
</tr>
<tr>
<td>11-15 yrs</td>
<td>(N=20)</td>
</tr>
<tr>
<td>Adult (N=17)</td>
<td>1726±12</td>
</tr>
</tbody>
</table>

**Volume of Distribution (Vd, L/kg) | Elimination Half-life (T1/2, hours) |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>2.2±0.7</td>
<td>1.5±0.2</td>
</tr>
<tr>
<td>3.5±2.6</td>
<td>2.3±0.4</td>
</tr>
<tr>
<td>3.1±0.2</td>
<td>1.5±0.2</td>
</tr>
</tbody>
</table>

Values are presented as means ± SD unless indicated otherwise.

**Values of pharmacokinetic parameters for pediatric patients are similar to those obtained for adults.**

Bioavailability studies of small numbers of pediatric patients (≤12 months) in eight patients, and there were no cases reported of erosion or ulceration of the esophagus. Famotidine was well tolerated at these doses. Famotidine was detectable in human milk. Because of the potential for serious adverse reactions in nursing infants from famotidine, data should not be administered to patients with a history of hypersensitivity to other H2-receptor antagonists.

**PRECAUTIONS:**

**Drug Interactions:**

The use of famotidine has been identified. Studies with famotidine in man, in animal models, and in vitro have shown no significant interaction with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds metabolized in man include warfarin, phenytoin, phenobarbital, diazepam, 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 2000 mg/kg/day (approximately 2500 times the recommended human dose for adult 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 metabolic activation. Values are presented as 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 without history of peptic ulcer disease, if there is no evidence of serious gastric ulcer, do not have to be hospitalized. Famotidine therapy should be continued for 2 to 4 weeks.

2. **Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer:** Patients who have had an ulcer but whose symptoms do not extend 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:** Famotidine injection 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:** For patients with 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. The drug should not be administered to patients with a history of hypersensitivity to other H2-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 reactions 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 (<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:**

The use of famotidine has been identified. Studies with famotidine in man, in animal models, and in vitro have shown no significant interaction with the disposition of compounds metabolized by the hepatic microsomal enzymes, e.g., cytochrome P450 system. Compounds metabolized in man include warfarin, phenytoin, phenobarbital, diazepam, and antipyrine. Indocyanine green as an index of hepatic drug extraction has been tested and no significant effects have been found.

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1. **Short term treatment of active duodenal ulcer:** Most adult patients within 4 weeks of admission, and decreased food intake were seen in some rabbits at oral doses of 200 mg/kg/day. (250 times the usual human dose). Moreover, in pregnant women, however, no adequate or well-controlled studies in pregnant women. Therefore, 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 mammalian toxic doses of at least 600 times the usual human dose. Famotidine is secreted into breast 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 1-16 years of age is supported by evidence from ade-
quate and well-controlled studies of famotidine in the treatment of peptic ulcer, data in pediatric patients are insufficient to establish percent response with dose and duration of therapy. Therefore, treatment duration (initially based on adult duration recommendations) and dose should be individualized based on clinical response and pH determination and endoscopy. Published uncontrolled studies in pediatric patients have demonstrated gastric acid suppression with doses up to 0.5 mg/kg intravenously or q 12 h.

No pharmacokinetic or pharmacodynamic data are available on pediatric patients under 1 year of age.

**Geriatric Use**

Of the 4,966 subjects in clinical studies who were treated with famotidine, 488 subjects (18%) were 65 and older, and 88 subjects (1.7%) were greater than 75 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects. However, greater sensitivity of some older individuals cannot be ruled out.

No dosage adjustment is required based on age.

**Dosage and Administration for Patients with Moderate or Severe Renal Insufficiency**

**ADVERSE REACTIONS:**

The adverse reactions listed below have been reported during domestic and international controlled clinical studies in adult patients and approximately 2500 patients in those controlled clinical trials in which famotidine tablets were compared to placebo, the incidence of these reactions in the group which received famotidine tablets, 40 mg at bedtime, was similar to that in the placebo group. The adverse reactions which have been reported to occur in more than 1% of patients on therapy with famotidine in controlled clinical trials are listed in Table 1. The incidence of the drug: headache (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhea (1.7%).

The following adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to the drug is unknown or uncertain. In the following list, the reactions are listed in order of decreasing severity.

**Body as a Whole:** fever, asthma, fatigue

**CNS:** hallucination

**Cardiovascular:** arrhythmia, AV block, palpitation

**Gastrointestinal:** cholestasis jaundice, liver enzyme elevations, vomiting, vivid dreams, abdominal discomfort, anorexia, dry mouth

**Hematologic:** rare cases of agranulocytosis, thrombocytopenia

**Hypersensitivity:** anaphylaxis, angioedema, orbital or facial edema, urticaria, rash, conjunctival injection

**Musculoskeletal:** musculoskeletal pain including myalgia, arthritis

**Nervous System/ Psychiatric:** grand mal seizure; psychiatric disturbances, which were reversible in cases for which follow-up was obtained, included agitation, depression, anxiety, decreased libido; paresthesia; insomnia; somnolence

**Respiratory:** cough

**Skin:** toxic epidermal necrolysis (very rare), alopecia, acne, pruritus, dry skin, flushing

**Special Senses:** tinnitus

**Vascular:** hypotension

**Other:** rare cases of impotence and rare cases of gynecomastia have been reported; however, in placebo controlled clinical trials, the incidences were not greater than those seen with placebo.

The adverse reactions reported for famotidine tablets may also occur with famotidine for oral suspension, famotidine orally disintegrating tablets, famotidine injection preserved free in plastic container or famotidine injection.

**OVERDOSAGE:**

There is no experience to date with deliberate overdosage. Oral doses of up to 440 mg/day have been given to adult 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 intravenous LD$_{50}$ of famotidine for mice and rats ranged from 254 to 563 mg/kg and the minimum lethal oral dose in dogs was approximately 300 mg/kg. Signs of acute intoxication in IV treated dogs were emesis, restlessness, pallor of mucous membranes, redness of mouth and ears, hypotension, tachycardia and collapse. The oral LD$_{50}$ of famotidine in male and female rats and mice was greater than 3000 mg/kg and the minimum lethal acute oral dose in dogs exceeded 20000 mg/kg. Famotidine did not produce overt effects at high oral doses in mice, rats, cats and dogs, but induced significant anorexia and weight loss in rabbits starting with 200 mg/kg/day orally.

**Dosage and Administration:**

In some hospitalized patients with pathological hypersecretory conditions, patients with severe renal insufficiency, or in patients who are unable to take oral medication, parenteral medication may be administered until oral therapy can be instituted. The recommended dosage for famotidine injection in adult patients is 20 mg intravenously q 12 h.

The doses and regimen for parenteral administration in patients with GERD have not been established.

**Dosage for Pediatric Patients**

See PRECAUTIONS, Pediatric Use.

**Dosage and Administration for Pediatric Patients with Moderate or Severe Renal Insufficiency**

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The doses and regimen for parenteral administration in patients with GERD have not been established.

**Dosage and Administration for Pediatric Patients with Moderate or Severe Renal Insufficiency**

In children 2 years of age or older, intravenous doses of 0.25 mg/kg intravenously (injected over a period of not less than two minutes or as a 15 minute infusion) q 12 h up to 40 mg/day.

While published uncontrolled clinical studies suggest effectiveness of famotidine in the treatment of pathological hypersecretory conditions in pediatric patients, these studies suggest that the starting dose for pediatric patients 1-16 years of age is 0.25 mg/kg intravenously (injected over a period of not less than two minutes or as a 15 minute infusion) q 12 h up to 40 mg/day.

**Concomitant Use of Antacids**

Antacids may be given concomitantly if needed.

**Stability**

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

When added to or diluted with most commonly used intravenous solutions, e.g., Water for Injection, 0.9% Sodium Chloride Injection, 5% and 10% Dextrose Injection, or Lactated Ringer’s Injection, diluted famotidine injection is physically and chemically stable (i.e., maintains at least 90% of initial potency) for 7 days at room temperature – see HOW SUPPLIED, STORAGE.

When added to or diluted with Sodium Bicarbonate Injection 5%, famotidine injection at a concentration of 0.2 mg/mL (the recommended concentration of famotidine intravenous infusion solution, see below) is physically and chemically stable (i.e., maintains at least 90% of initial potency) for 7 days at room temperature – see HOW SUPPLIED, STORAGE. However, a precipitate may form at higher concentrations of famotidine injection (>0.2 mg/mL) in Sodium Bicarbonate Injection, 5%.

**HOW SUPPLIED:** FOR INTRAVENOUS USE ONLY AFTER DILUTION

Famotidine Injection 10 mg per 1 mL is a non-preserved, clear, colorless solution and is supplied as:

- Product NDC No. No. 730912 63323-739-12
- Famotidine Injection, 10 mg/mL, 2 mL single dose vial, 25 vials per tray

**Storage**

Store famotidine injection at 2-8°C (36-46°F). If solution freezes, bring to room temperature; allow sufficient time to solubilize all the components.

Although diluted famotidine injection has been shown to be physically and chemically stable for 7 days at room temperature, there are no data on the maintenance of sterility after dilution. Therefore, do not use immediately after preparation, diluted solutions of famotidine injection should be refrigerated and used within 24 hours – see DOSAGE AND ADMINISTRATION.

Vial stoppers do not contain natural rubber latex.