PRESCRIBING INFORMATION

[Pr] FAMOTIDINE INJECTION

10 mg/mL

(40 mg/4 mL, 200 mg/20 mL)

Histamine H_2 Receptor Antagonist

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PACKAGE INSERT

PrFAMOTIDINE INJECTION

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(40 mg/4 mL, 200 mg/20 mL)

Histamine H_2 Receptor Antagonist

CLINICAL PHARMACOLOGY

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

INDICATIONS

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.

Famotidine is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication. 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

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 30-50 mL/min) or severe (creatinine clearance <30 mL/min) renal insufficiency to adjust for the longer elimination half-life of famotidine (see **HUMAN PHARMACOLOGY, Pharmacokinetics** 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 Famotidine Injection. Symptomatic response of gastric ulcer to therapy with Famotidine Injection 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 Famotidine Injection in pregnant women has not been established, the benefits of treatment with Famotidine Injection 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**). This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function. Dosage adjustment in the case of moderate or severe renal impairment is necessary (see **PRECAUTIONS, Patients with Moderate or Severe Renal Insufficiency** and **DOSAGE AND ADMINISTRATION, Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency**).

ADVERSE REACTIONS

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 tablets, 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 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 including muscle cramps	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%**

In addition, transient irritation at the injection site has been observed with Famotidine Injection.

The following additional adverse reactions have been reported since the drug was marketed: urticaria, liver enzymes abnormalities, cholestatic jaundice, anaphylaxis, angioedema. Toxic epidermal necrolysis has been reported very rarely with H_2 receptor antagonists. As with other H_2-receptor antagonists, cases of bradycardia, A-V block and other arrhythmias have been reported rarely in patients treated with famotidine.
The following adverse reactions have been reported; however, a causal relationship to therapy with Famotidine Injection 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.

DOSAGE AND ADMINISTRATION

Intravenous Administration

In some hospitalized patients with pathological hypersecretory conditions or intractable ulcers, or in patients who are unable to take oral medication, Famotidine Injection may be administered. The recommended dosage is 20 mg every 12 hours.

Intravenous injection therapy should be changed to oral treatment as soon as the acute situation is under control.

Concomitant Use with Antacids

Antacids may be given concomitantly if needed.

Dosage Adjustment for Patients with Moderate or Severe Renal Insufficiency

In patients with moderate (creatinine clearance 30-50 mL/min) or severe (creatinine clearance <30 mL/min) renal insufficiency, the elimination half-life of famotidine is increased. For patients with severe renal insufficiency, it may exceed 20 hours, reaching approximately 24 hours in anuric patients. Since CNS adverse reactions have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate or severe renal insufficiency, the dose of famotidine may be reduced to half the dose or the dosing interval may be prolonged to 36-48 hours as indicated by the patient's clinical response.

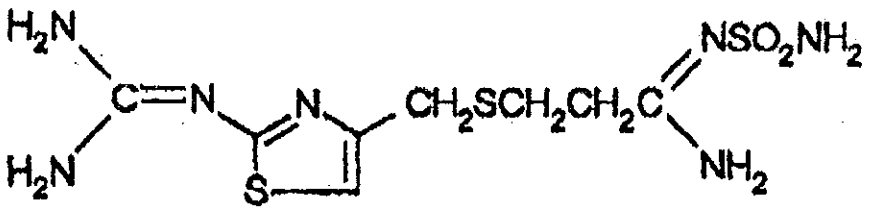
PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Famotidine

Chemical name: Propanimidamide -(aminosulfonyl)-3-[[[2-[(diaminomethylene)amino]-4-thiazolyl]methyl]thio] .

Structural formula:



Molecular formula: $C_8H_{15}N_7O_2S_3$

Molecular weight 337.44

Melting point: 163-164° C

pH: 7.40 (saturated solution at 25°C, I=0.01)

pKa: 6.3

Description: 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.

Composition

Each mL of the solution for intravenous injection contains 10 mg of Famotidine and the following non-medicinal ingredients: L-Aspartic Acid 4 mg, Mannitol 20 mg, and Water for Injection, q.s., 1 mL. Each mL of the solution also contains 9 mg of Benzyl Alcohol as preservative.

Stability and Storage Recommendations

Store at 2-8°C. Protect from light. If solution freezes, bring the solution to room temperature; allow sufficient time to solubilize all the components.

The in-use stability period for the Famotidine Injection (multidose vials), following initial puncture of the stopper, is 6 days.

Parenteral Solutions

Dilution of Famotidine for Infusion

Famotidine Injection	Volume of Compatible I.V. Solution	Final Volume	Final concentration	Rate of Infusion
2 mL	3 mL	5 mL	4 mg/mL	Not less than 2 minutes
2 mL	8 mL	10 mL	2 mg/mL	Not less than 2 minutes
2 mL	100 mL	102 mL	0.196 mg/mL	15-30 minutes

Famotidine Injection solutions are compatible with:

Sterile Water for Injection, USP (in 500 mL PVC bags)

0.9% Sodium Chloride Injection, USP (in 250 mL PVC bags)

5% Dextrose Injection, USP (in 250 mL PVC bags)

10% Dextrose Injection, USP (in 250 mL PVC bags)
Lactated Ringer's Injection, USP (in 500 mL PVC bags)

Diluted Famotidine Injection solution should be used within 24 hours due to the possibility of microbial contamination during preparation.

Only institutions with recognized intravenous admixture programs should store the infusions up to 7 days.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portions.

AVAILABILITY OF DOSAGE FORMS

Famotidine Injection, 10 mg/ mL is available as 40 mg/4 mL and 200 mg/20mL multi-dose vials in individual cartons.

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