Name of the Medicine

Famotidine

Chemical name: 3-[[2-[(aminoiminomethyl) amino]-4-thiazolyl]methylthio]-N- (aminosulphonyl) propanimidamide.

Structural formula:

\[
\text{H}_2\text{NNN} \quad \text{SN} \quad \text{NH}_2 \quad \text{S} \quad \text{S} \quad \text{NH}_2 \quad \text{OO} 
\]

Molecular formula : \( \text{C}_{8}\text{H}_{15}\text{N}_{7}\text{O}_{2}\text{S}_{3} \)  
Molecular weight : 337.43  
CAS Registry No.: 76824-35-6

Description

Famotidine is a white to pale yellow non-hygroscopic crystalline substance. It is very slightly soluble in water and practically insoluble in ethanol, acetone, ethylacetate, ethyl ether and chloroform. It is freely soluble in glacial acetic acid.

Each Pamacid 20 tablet contains 20 mg famotidine. The tablets also contain pregelatinised maize starch, microcrystalline cellulose, purified talc, magnesium stearate, lactose, hypromellose, titanium dioxide, and glycerol triacetate.

Each Pamacid 40 tablet contains 40 mg famotidine. The tablets also contain pregelatinised maize starch, microcrystalline cellulose, purified talc, magnesium stearate, lactose, hypromellose, glycerol triacetate, iron oxide red CI77491, iron oxide yellow CI77492 and titanium dioxide.

Pharmacology

Gastrointestinal Effects

Famotidine is a competitive inhibitor of histamine \( \text{H}_2 \)-receptors. The primary clinically important pharmacological 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 ten to twelve hours.
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 ten hours. The same doses given in the morning suppressed food-stimulated acid secretion in all subjects. The mean suppression was 76% and 84% respectively three to five hours after administration, and 25% and 30% respectively eight to ten hours after administration. However, in some subjects who received the 20 mg dose the antisecretory effect was dissipated within six to eight hours. Clinical efficacy studies have not been carried out with a 20 mg dose in acute ulceration. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20mg 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 three and eight hours after 20 or 40 mg of famotidine was raised to about 5.

The presence of gastro-oesophageal reflex disease appears to correlate best with the percentage of time over 24 hours during which the oesophagus is exposed to acid. In patients with gastro-oesophageal reflex disease, 20 mg twice daily and 40 mg twice daily of famotidine reduced intra-oesophageal acid exposure into the normal range as measured by 24 hour intra-oesophageal pH monitoring.

In a clinical study of patients with gastro-oesophageal reflux disease with endoscopically verified erosive or ulcerative oesophagitis famotidine 20 mg twice daily and 40 mg twice daily were superior to placebo and 40 mg twice daily was statistically significantly more effective than 20 mg twice daily in healing oesophageal lesions. In another study however, the results for the 40 mg twice daily group were similar to the results for the 20 mg twice daily group.

In patients treated for six months with famotidine 20 mg twice daily, relapse of oesophageal erosions or ulceration was significantly less than in patients treated with placebo. Famotidine was also shown to be superior to placebo in preventing symptomatic deterioration.

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

Other effects
Systemic effects of famotidine in the central nervous system, cardiovascular, respiratory or endocrine systems have not been found to date. No anti-androgenic effects have been detected.

Pharmacokinetics
Famotidine is incompletely absorbed and undergoes minimal first-pass metabolism. The bioavailability of oral doses is 40% to 45% and may be slightly increased by food or slightly decreased by antacids; however, these effects are of no clinical consequence. After oral doses, peak plasma levels occur in one to three 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 and is eliminated by renal (65% to 70%) and metabolic (30% to 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 dose or dosing intervals, in moderate and severe renal insufficiency, may be necessary (see Precautions, Dosage and Administration).

Renal excretion increases in a dose-dependent linear fashion, but the area under the curve (AUC) and Cmax are not dose-proportional. Further studies may be required to define the kinetics of famotidine.

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, Dosage and Administration).
Hepatic dysfunction does not appear to alter famotidine pharmacokinetics. In a study comparing eleven patients with alcohol-related cirrhosis to five healthy control subjects, there were no significant between-group differences in famotidine pharmacokinetics following single oral 20 mg doses, or multiple (once daily for seven days) oral 40 mg doses.

**Indications**

- Duodenal ulcer.
- Benign gastric ulcer.
- Zollinger-Ellison Syndrome.
- Prevention of relapses of duodenal ulceration.
- Short term (no more than 12 weeks) symptomatic relief of gastro-oesophageal reflux not responsive to conservative measures.
- Healing of oesophageal erosion or ulceration associated with gastro-oesophageal reflux disease.
- Prevention of relapses of symptoms and erosions or ulcerations associated with gastro-oesophageal reflux disease.

**Contraindications**

Hypersensitivity to famotidine or any component of these products. 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 H₂-receptor antagonists.

**Precautions**

**Gastric Neoplasm**

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

**Intensive Care Units**

Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

**Community acquired pneumonia**

In patients such as the elderly, persons with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H₂-receptor antagonists versus those that had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07-2.48).

**Impaired renal function**

CNS adverse effects have been reported in patients with moderate (creatinine clearance < 50 mL/min) and severe (creatinine clearance < 10 mL/min) renal insufficiency. Consequently, the famotidine dosage should be reduced in patients with moderate or severe renal impairment (see Pharmacology and Dosage and Administration).

**Impaired hepatic function**

See pharmacokinetics.
Use In the Elderly

No dosage adjustment is required based on age alone. When famotidine was administered to elderly patients in clinical trials, no increase in the incidence or change in the type of adverse effects was observed. As elderly patients are more likely to have decreased renal function, care should be taken in dose selection in this patient group, and it may be useful to monitor renal function (see Precautions; Impaired renal function, Dosage and Administration).

Use in Pregnancy (Category B1)

Famotidine has been demonstrated to cross the placenta and enter the foetus when administered to pregnant rats.

Famotidine has not shown teratogenic effects when given to pregnant rats at doses up to 2000 mg/kg orally or up to 200 mg/kg intravenously, or in rabbits at oral doses up to 500 mg/kg and 100 mg/kg intravenously.

Famotidine did not appear to affect the fertility of rats at oral doses up to 2000 mg/kg or intravenous doses up to 200 mg/kg.

Famotidine is not recommended for use in pregnancy and should be prescribed only if clearly needed. The physician should weigh the potential benefits from the drug against the possible risks involved before a decision is made to use famotidine during pregnancy.

Use in Lactation

Famotidine is detectable in human milk. Breastfeeding mothers should either stop this drug or stop breastfeeding.

Paediatric Use

Safety and effectiveness of famotidine in children have not been established.

Interactions with Other Medicines

No drug interactions of clinical importance have been identified. Famotidine does not interact with the cytochrome P450-linked drug metabolising enzyme system. Compounds metabolised by this system which have been tested in man in short term studies include warfarin, propranolol, 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.

A study of eleven patients stabilised on phenprocoumon therapy have shown no pharmacokinetic interaction with famotidine and no effect on the pharmacokinetic or anticoagulant activity of phenprocoumon.

Adverse Effects

Famotidine has been shown to be generally well-tolerated. Headache, dizziness, constipation and diarrhoea have been reported at a frequency of greater than 1% in controlled clinical trials and may be causally related to famotidine. A similar incidence of the same effects was seen in the placebo or active comparison arms of these studies.

Rarely reported events included dry mouth, nausea and/or vomiting, rash, abdominal discomfort or distension, anorexia, fatigue, pruritus, urticaria, liver enzymes abnormalities, cholestatic jaundice, anaphylaxis, angioedema, arthralgia, muscle cramps, taste disorder, thrombocytopenia, leucopenia, neutropenia, reversible psychic disturbances including depression, anxiety disorders, agitation, confusion and hallucinations. Interstitial pneumonia and Stevens Johnson Syndrome / toxic epidermal necrolysis has been reported very rarely with H2-receptor antagonists. Convulsions in patients with impaired renal function have been reported very rarely.
The following side effects have been reported, however, a causal relationship to therapy with famotidine has not been established: decreased libido, paraesthesia, somnolence, insomnia, grand mal seizure, pancytopenia, agranulocytosis. Rare cases of impotence and rare cases of gynaecomastia have been reported, however, in controlled clinical trials the incidences were not greater than that seen with placebo.

**Dosage and Administration**

**Duodenal Ulcer**

Initial Therapy: The recommended dose of famotidine is 40 mg daily taken at night for four to eight weeks. The duration of treatment may be shortened if endoscopy reveals that the ulcer has healed. In most cases of duodenal ulcer, healing occurs within four weeks on this regimen. In those patients whose ulcers have not healed completely after four weeks, treatment should be continued for a further four week period.

Maintenance Therapy: For the prevention of recurrence of duodenal ulceration, it is recommended that therapy with famotidine be continued with a dose of 20 mg daily taken at night. In ongoing clinical studies this regimen has been continued for twelve months.

**Benign Gastric Ulcer**

The recommended dose of famotidine is one 40 mg tablet daily, taken at night. Treatment should be given for four to eight weeks, but the duration of treatment may be shortened if endoscopy reveals that the ulcer has healed.

**Zollinger-Ellison Syndrome**

Patients without prior antisecretory therapy should be started on a dose of 20 mg every six hours. Dosage should be adjusted to individual patient needs and should continue for as long as indicated clinically. Doses up to 800 mg daily have been used in a small number of patients for up to one year without the development of significant adverse effects or tachyphylaxis. Patients who have been receiving another H₂ antagonist may be switched directly to famotidine at a starting dose higher than that recommended for new cases; this starting dose will depend on the severity of the condition and the last dose of the H₂ antagonist previously used.

**Gastro-oesophageal Reflux Disease**

The recommended dosage for the symptomatic relief of gastro-oesophageal reflux disease is 20 mg of famotidine taken orally twice daily.

For the treatment of oesophageal erosion or ulceration associated with gastro-oesophageal reflux disease, the recommended dosage is 20 mg of famotidine twice daily.

Maintenance Therapy: For the prevention of recurrence of symptoms and erosions or ulcerations associated with gastro-oesophageal reflux disease, the recommended dosage is 20 mg of famotidine twice daily. Efficacy studies have not been conducted beyond six months.

**Impaired renal function**

In patients with moderate (creatinine clearance < 50 mL/min) and severe (creatinine clearance < 10 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 effects have been reported in patients with moderate and severe renal insufficiency, to avoid excess accumulation of the drug in patients with moderate and severe renal insufficiency, the dose of famotidine may be reduced to half the dose or the dosing interval may be prolonged to 36 to 48 hours as indicated by the patient's clinical response.
Overdosage

The adverse reactions in overdose cases are similar to the adverse reactions encountered in normal clinical experience (see Adverse Effects).

Doses of up to 800 mg daily have been used in a small number of patients with Zollinger-Ellison Syndrome for more than a year without development of significant adverse effects.

The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring and supportive therapy should be employed.

Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of overdosage.

Presentation and Storage Conditions

*Pamacid 20*  white, film-coated, D-shaped, biconvex tablet marked with “G” on one side and “FD” over “20” on the other; blister packs and bottles of 60 tablets.

*Pamacid 40* light-brown, film-coated, scored, diamond-shaped, biconvex tablet marked with “G | G” on one side and “FD40” on the other; blister packs and bottles of 30 tablets.

Store below 25°C.

Poison Schedule of the Medicine

S4 (Prescription Only Medicine)

Name and Address of the Sponsor

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Date of Approval

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