NAME OF THE MEDICINE
Famotidine.

Chemical Name: 3-[[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(aminosulfonyl)propanimidamide. It is a guanylthiazole derivative.

Structural Formula:

![Structural formula image]

Molecular Formula: \( C_8H_{15}N_7O_2S_3 \)
Molecular Weight: 337.45
CAS Registry Number: 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, ethyl acetate, ether and chloroform. It is freely soluble in glacial acetic acid.

PHARMACOLOGY
Pharmacokinetics
Famotidine is incompletely absorbed. The bioavailability of oral doses is 40 to 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. 15 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. 25 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 humans 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, single intravenous
Product Information – Australia

20 mg doses or multiple (once daily for seven days) oral 40 mg doses.

**Pharmacodynamics**

**Gastrointestinal Effects**

Famotidine is a competitive inhibitor of histamine H₂-receptors. The primary clinically important pharmacological activity of famotidine is inhibition of gastric secretion. Both the acid concentration and volume of basal, nocturnal and stimulated 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 anti-secretory 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 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. In some subjects who received the 20 mg dose, however, the anti-secretory 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 is no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of famotidine 20 and 40 mg 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 famotidine 20 or 40 mg was raised to about 5.

The presence of gastro-oesophageal reflux 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 reflux disease, famotidine 20 and 40 mg twice daily reduced intraoesophageal acid exposure into the normal range as measured by 24 hour intraoesophageal pH monitoring. In a clinical study of patients with gastro-oesophageal reflux disease with endoscopically verified erosive or ulcerative oesophagitis, famotidine 20 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 postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by famotidine.

**Other Effects**

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

**INDICATIONS**

- The treatment of 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 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

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 who had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07–2.48).

Gastric Neoplasm
Gastric malignancy should be excluded prior to initiation of therapy of gastric ulcer with famotidine. Symptomatic response of gastric ulcer to therapy with famotidine 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 intensive care unit patients receiving mechanical ventilation.

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 insufficiency (see PHARMACOLOGY, and DOSAGE AND ADMINISTRATION).

Impaired Hepatic Function: see PHARMACOLOGY, Pharmacokinetics.

Effects on fertility
In studies with rats given oral doses of up to 2000 mg/kg/day or intravenous doses of up to 200 mg/kg/day, fertility and reproductive performance were not affected.

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

Category B1: Drugs that have been taken by only a limited number of pregnant women and women of childbearing age without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

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

Use in Children
Safety and effectiveness of famotidine in children has not been established.
Use in the Elderly
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. No dosage adjustment is required based on age alone. 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, Renal Impairment and DOSAGE AND ADMINISTRATION).

Carcinogenesis/Mutagenesis
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 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 μg/plate. In in vivo studies in mice, with a micronucleus test and a chromosomal aberration test, no evidence of a mutagenic effect was observed.

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 humans 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 has 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.

The following adverse reactions have been reported to occur in more than 1% of patients on therapy with famotidine in controlled clinical trials and may be causally related to the drug: Headaches (4.7%), dizziness (1.3%), constipation (1.2%) and diarrhoea (1.7%)

A similar incidence of the same effects was seen in the placebo or active comparison arms of these studies.

The following other adverse reactions have been reported infrequently in clinical trials or since the drug was marketed. The relationship to therapy with famotidine has been unclear in many cases. Within each category the adverse reactions are listed in order of decreasing severity:

Body as a Whole
Fever, asthenia, fatigue.

Cardiovascular
Arrhythmia, atrioventricular block, palpitations.

Gastrointestinal
Cholestatic jaundice, liver enzyme abnormalities, nausea, vomiting, abdominal discomfort or distension, anorexia, dry mouth.

Haematologic
Rare cases of agranulocytosis, pancytopenia, leucopenia, thrombocytopenia.

Hypersensitivity
Anaphylaxis, angioedema, orbital or facial oedema, urticaria, rash, conjunctival injection.
Musculoskeletal
Musculoskeletal pain including muscle cramps, arthralgia.

Central Nervous System
Grand mal seizure, reversible psychic disturbances including hallucinations, confusion, agitation, depression, anxiety, decreased libido, paraesthesia, insomnia, somnolence. Convulsions in patients with impaired renal function have been reported very rarely.

Respiratory
Bronchospasm, interstitial pneumonia.

Dermatological
Toxic epidermal necrolysis (very rare), Stevens Johnson syndrome (very rare), alopecia, acne, pruritus, dry skin, flushing.

Special Senses
Tinnitus, taste disorder.

Other
Rare cases of impotence and gynaecomastia have been reported, however, in controlled clinical trials, the incidences were not greater than seen with placebo.

DOSAGE AND ADMINISTRATION

Heartburn, Dyspepsia and Indigestion
One tablet as needed when symptoms occur, or one tablet 30 to 60 minutes before eating for symptoms usually associated with food or beverage. Do not take more than two tablets in a 24 hour period. If symptoms persist beyond five days or is symptoms recur within two weeks of completing a course, clinical investigation is required.

Duodenal Ulcer
Initial Therapy
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. In most cases, 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 one 20 mg tablet 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 with prior anti-secretory 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 famotidine
20 mg taken orally twice daily.

For the treatment of oesophageal erosion or ulceration associated with gastro-oesophageal reflux disease, the recommended dosage is famotidine 20 mg 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 famotidine 20 mg twice daily. Efficacy studies have not been conducted beyond six months.

**Impaired Renal Function**

In patients with moderate (creatinine clearance < 50 mL/min) or 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 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.

**OVERDOSE**

**Symptoms**

There is no experience to date with overdose. 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.

**Treatment**

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

**Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdose.**

**PRESENTATION AND STORAGE CONDITIONS**

**Terry White Chemists Famotidine 20 mg Tablets**

A beige, round, biconvex tablet embossed with 20 on one face and plain on the other.

Blister packs containing 60 tablets

AUST R number 91511

**Terry White Chemists Famotidine 40 mg Tablets**

A brown, round, biconvex tablet embossed with 40 on one face and plain on the other.

Blister packs containing 30 tablets

AUST R number 91512

Terry White Chemists Famotidine 20 mg and 40 mg Tablets are intended for oral administration. Each tablet contains famotidine 20 mg or 40 mg.

In addition, each tablet contains the following inactive ingredients:

- Pregelatinised maize starch, microcrystalline cellulose, magnesium stearate, purified talc, Opadry Buff OY-3690 (20 mg only) and Opadry Buff OY-3682 (40 mg only).

Store below 30°C, protect from light and moisture.

**NAME AND ADDRESS OF THE SPONSOR**

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Australia
NAME AND ADDRESS OF THE DISTRIBUTOR
Symbion Pharmacy Services Pty Ltd
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Noble Park North VIC 3174
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Terry White Chemists is a registered trade mark of Symbion Pharmacy Services Pty Ltd.

POISON SCHEDULE OF THE MEDICINE
S4: Prescription Only Medicine.

Date of TGA approval: 14 October 2002
Date of most recent amendment: 2 August 2011