PRODUCT INFORMATION

Tablets

PEPCIDINE®
(Famotidine, MSD)

INTRODUCTION

PEPCIDINE (famotidine, MSD) is a competitive inhibitor of histamine H₂-receptors. The primary clinically important pharmacological activity of PEPCIDINE is inhibition of gastric juice secretion. PEPCIDINE reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretion.

DESCRIPTION

PEPCIDINE (famotidine, MSD) is 3-[[2-[(aminoiminomethyl) amino]-4-thiazolyl]methyl]thio]-N-(aminosulphonyl) propanimidamide. It is a guanylthiazole derivative with an empirical formula of C₈ H₁₅ N₇ O₂ S₃ and its structural formula is:

![Structural formula of Famotidine]

Famotidine is a white to pale yellow non-hygroscopic crystalline substance with a molecular weight of 337.43. 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.
PHARMACOLOGY

PHARMACODYNAMICS

Gastrointestinal Effects

PEPCIDINE is a competitive inhibitor of histamine H₂-receptors. The primary clinically important pharmacological activity of PEPCIDINE is inhibition of gastric secretion. Both the acid concentration and volume of gastric secretion are suppressed by PEPCIDINE, while changes in pepsin secretion are proportional to volume output.

In normal volunteers and hypersecretors, PEPCIDINE 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 40mg was 10 to 12 hours.

Single evening oral doses of 20 and 40mg 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 20mg dose, however, the antisecretory effect was dissipated within 6 - 8 hours. Clinical efficacy studies have not been carried out with a 20mg dose in acute ulceration. There was no cumulative effect with repeated doses. The nocturnal intragastric pH was raised by evening doses of 20 and 40mg of PEPCIDINE to mean values of 5.0 and 6.4 respectively. When PEPCIDINE was given after breakfast, the basal daytime interdigestive pH at 3 and 8 hours after 20 or 40mg of PEPCIDINE was raised to about 5.

The presence of gastroesophageal 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 gastroesophageal reflux disease, 20mg b.d. and 40mg b.d. of PEPCIDINE reduced intraesophageal acid exposure into the normal range as measured by 24 hour intraesophageal pH monitoring.

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

In patients treated for 6 months with PEPCIDINE 20mg b.d., relapse of oesophageal erosions or ulceration was significantly less than in patients treated with placebo. PEPCIDINE was also shown to be superior to placebo in preventing symptomatic deterioration.
PEPCIDINE had little or no effect on fasting or postprandial serum gastrin levels. Gastric emptying and exocrine pancreatic function were not affected by PEPCIDINE.

**Other effects**

Systemic effects of PEPCIDINE in the CNS, cardiovascular, respiratory or endocrine systems have not been found to date. No anti-androgenic effects have been detected.

**PHARMACOKINETICS**

PEPCIDINE is incompletely absorbed. The bioavailability of oral doses is 40-45%. Bioavailability may be slightly increased by food, or slightly decreased by antacids; however, these effects are of no clinical consequence. PEPCIDINE undergoes minimal first-pass metabolism. After oral doses, peak plasma levels occur in 1-3 hours. Plasma levels after multiple doses are similar to those after single doses. Fifteen to 20% of PEPCIDINE in plasma is protein bound. PEPCIDINE has an elimination half-life of 2.5-3.5 hours. PEPCIDINE is eliminated by renal (65-70%) and metabolic (30-35%) routes. Renal clearance is 250-450mL/min, indicating some tubular excretion. Twenty-five to 30% of an oral dose and 65-70% 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 PEPCIDINE. In patients with severe renal insufficiency, i.e. creatinine clearance less than 10mL/min, PEPCIDINE 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 AUC and C\text{max} 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 PEPCIDINE. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (see PRECAUTIONS AND DOSAGE AND ADMINISTRATION).

**LIVER DYSFUNCTION**

Hepatic dysfunction does not appear to alter famotidine pharmacokinetics. In a study comparing 11 patients with alcohol-related cirrhosis to 5 healthy control subjects, there were no significant between-group differences in famotidine pharmacokinetics following single oral 20 mg doses, single i.v. 20 mg dose, or multiple (once daily for 7 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 gastroesophageal reflux not responsive to conservative measures.
- Healing of oesophageal erosion or ulceration associated with gastroesophageal reflux disease.
- Prevention of relapses of symptoms and erosions or ulcerations associated with gastroesophageal reflux disease.

CONTRAINDICATIONS

Hypersensitivity to any component of these products. Cross sensitivity in this class of compounds has been observed. Therefore, PEPCIDINE 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 PEPCIDINE. Symptomatic response of gastric ulcer to therapy with PEPCIDINE does not preclude the presence of gastric malignancy.

Renal Insufficiency

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 & 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 2000mg/kg orally or up to 200mg/kg intravenously, or in rabbits at oral doses up to 500mg/kg and 100mg/kg intravenously.
Famotidine did not appear to affect the fertility of rats at oral doses up to 2000mg/kg or intravenous doses up to 200mg/kg.

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

Use in Lactation

Famotidine is detectable in human milk. Breast feeding mothers should either stop this drug or stop breast feeding.

Paediatric Use

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

Use in the Elderly

When PEPCIDINE 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 Insufficiency and DOSAGE & ADMINISTRATION).

Driving and Operating Machinery

PEPCIDINE may cause certain adverse effects such as dizziness, confusion, or hallucinations and therefore, patients should know how they react to PEPCIDINE before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination (see ADVERSE EFFECTS).

Interactions with other Medicines

No drug interactions of clinical importance have been identified. PEPCIDINE 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 11 patients stabilised on phenprocoumon therapy has shown no pharmacokinetic interaction with famotidine and no effect on the pharmacokinetic or anticoagulant activity of phenprocoumon.

Intensive Care Units

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

PEPCIDINE 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, alopecia, liver enzyme abnormalities, hepatitis, cholestatic jaundice, anaphylaxis, angioedema, arthralgia, muscle cramps, taste disorder, reversible psychic disturbances including depression, anxiety disorders, agitation, confusion, hallucinations, thrombocytopenia, leukopenia, neutropenia, and agranulocytosis. Interstitial pneumonia and Stevens Johnson syndrome / toxic epidermal necrolysis have been reported very rarely with H₂-receptor antagonists. In patients with impaired renal function, the following have been reported very rarely: convulsions, prolonged QT interval.

The following side effects have been reported, however, a causal relationship to therapy with PEPCIDINE has not been established: decreased libido, paraesthesia, somnolence, insomnia, grand mal seizure, pancytopenia. 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 & ADMINISTRATION

DUODENAL ULCER

Initial Therapy

The recommended dose of PEPCIDINE is one 40mg 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 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 PEPCIDINE be continued with a dose of one 20mg tablet daily taken at night. In ongoing clinical studies this regimen has been continued for twelve months.

BENIGN GASTRIC ULCER

The recommended dose of PEPCIDINE is one 40mg 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 20mg 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 PEPCIDINE 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.

GASTROESOPHAGEAL REFLUX DISEASE

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

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

Maintenance of Therapy:

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

DOSAGE ADJUSTMENT FOR PATIENTS WITH MODERATE OR SEVERE RENAL INSUFFICIENCY

In patients with moderate (creatinine clearance < 50 mL/min) or severe (creatinine clearance < 10 mL/min) renal insufficiency, the elimination half life of PEPCIDINE 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 PEPCIDINE 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.

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 for advice on management.
PRESENTATION AND STORAGE CONDITIONS

PEPCIDINE 40mg, tan (light brownish-orange), rounded square, film-coated tablets, one side engraved with "MSD 964" and the other side plain. Supplied in blister packs of 30 tablets.

PEPCIDINE M 20mg, beige, rounded square, film-coated tablets, one side engraved with "MSD 963" and the other side plain. Supplied in blister packs of 60 tablets.

Store below 30°C

POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (S4).

NAME AND ADDRESS OF SPONSOR

Merck Sharp & Dohme (Australia) Pty. Limited
54-68 Ferndell St., South Granville, N.S.W., 2142

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