

# New Zealand Data Sheet



## 1. PRODUCT NAME

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Pepzan® 20 mg and 40 mg tablet

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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Each Pepzan 20 mg tablet contains famotidine 20 mg.

Each Pepzan 40 mg tablet contains famotidine 40 mg.

### Excipient(s) with known effect

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

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Pepzan 20 mg tablet is a beige, square, biconvex tablet of 7.1mm length on one side embossed with 20 on one face and the company monogram on the other.

Pepzan 40 mg tablet is a brown, square, biconvex tablet of 7.1mm length on one side embossed with 40 on one face and the company monogram on the other.

## 4. CLINICAL PARTICULARS

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### 4.1. Therapeutic indications

- Duodenal ulcer
- Benign gastric ulcer
- Hypersecretory conditions such as Zollinger-Ellison syndrome
- Prevention of relapses of duodenal ulceration
- Prevention of relapses of benign gastric ulcer
- Symptomatic relief of gastroesophageal reflux disease
- Healing of oesophageal erosion or ulceration associated with gastroesophageal reflux disease
- Prevention of relapses of symptoms and erosions or ulcerations associated with GERD

### 4.2. Dose and method of administration

#### 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 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 one 20 mg tablet daily taken at night.

### **Benign gastric ulcer**

The recommended dose of famotidine is one 40 mg tablet daily taken at night. Treatment should be given for 4 - 8 weeks, but the duration of treatment may be shortened if endoscopy reveals that the ulcer has healed.

### ***Maintenance therapy***

For the prevention of recurrence of benign gastric ulcer, the recommended dosage is one 20 mg tablet taken at night which may be given for up to one year.

### **Zollinger-Ellison syndrome**

Patients without prior antisecretory therapy should be started on a dose of 20 mg every 6 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 for up to one year without the development of significant adverse effects or tachyphylaxis. Patients who have been receiving another H<sub>2</sub>-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 H<sub>2</sub>-antagonist previously used.

### **Gastroesophageal reflux disease**

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

For the treatment of oesophageal erosion or ulceration associated with GERD, the recommended dosage is 40 mg of famotidine twice daily.

### ***Maintenance therapy***

For the prevention of recurrence of symptoms and erosions or ulcerations associated with GERD the recommended dosage is 20 mg of famotidine twice daily.

### **Special population**

#### ***Severe renal insufficiency***

In adult 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 medicine 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 - 48 hours as indicated by the patient's clinical response (refer to section 4.4).

### **4.3. 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 H<sub>2</sub>-receptor antagonists.

### **4.4. Special warnings and precautions for use**

#### **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.

#### **Renal Dysfunction**

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 (refer to section 4.2 and 5.2).

#### **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 medicine related side 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 (refer to section 4.2 and 4.4).

#### **Paediatric use**

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

#### **Intensive care units**

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

#### **4.5. Interaction with other medicines and other forms of interaction**

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 11 patients stabilised on phenprocoumon therapy has shown no pharmacokinetic interaction with famotidine and no effect on the pharmacokinetic or anticoagulant activity of phenprocoumon.

#### **4.6. Fertility, pregnancy and lactation**

##### **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 2000mg/kg or intravenous doses up to 200mg/kg.

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 physician should weigh the potential benefits from the medicine against the possible risks involved.

##### **Breast-feeding**

Famotidine is detectable in human milk. Nursing mothers should either stop this medicine or should stop breast feeding.

##### **Fertility**

No data available.

#### **4.7. Effects on ability to drive and use machines**

Famotidine may cause certain adverse effects such as dizziness, confusion or hallucinations and therefore, patients should know how they react to famotidine before they operate an automobile or machinery or engage in activities requiring mental alertness and coordination (refer to section 4.8).

#### **4.8. Undesirable effects**

Famotidine has been demonstrated 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 and hallucinations, thrombocytopenia, leukopenia and neutropenia. Interstitial pneumonia and Stevens Johnson syndrome/toxic epidermal necrolysis have been reported very rarely with H<sub>2</sub>-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; and agranulocytosis. Rare cases of impotence and rare cases of gynaecomastia have been reported. However, in controlled clinical trials the incidences were not greater than those seen with placebo.

### **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected reactions <https://nzphvc.otago.ac.nz/reporting/>

### **4.9. Overdose**

The adverse reactions in overdose cases are similar to the adverse reactions encountered in normal clinical experience (refer to section 4.8).

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

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

## **5. PHARMACOLOGICAL PROPERTIES**

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### **5.1. Pharmacodynamic properties**

Pharmacotherapeutic group: drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD), ATC code: A02BA03

## **Actions**

Pepzan (famotidine) is a competitive inhibitor of histamine H<sub>2</sub>-receptors. The primary clinical important pharmacologically activity of famotidine is inhibition of gastric juice secretion. Famotidine reduces the acid and pepsin content, as well as the volume of basal, nocturnal and stimulated gastric secretions.

### **5.2. Pharmacokinetic properties**

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 mg and 40 mg was 10 to 12 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 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 20 mg dose in acute ulceration. 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 inter-digestive pH at 3 and 8 hours after 20 or 40 mg of famotidine was raised to about 5.

The presence of gastroesophageal reflux disease (GERD) 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, 20 mg twice daily and 40 mg twice daily of famotidine reduced intraoesophageal acid exposure into the normal range as measured by 24-hour intraoesophageal pH monitoring.

In a clinical studies of patients with gastroesophageal 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 group.

In patients treated for 6 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.

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

Famotidine 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. Famotidine 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. 15 - 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 - 70 %) and metabolic (30 - 35 %) routes. Renal clearance is 250 - 450 mL/min, indicating some tubular excretion. 25 - 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 famotidine. In patients with severe renal insufficiency (creatinine clearance <10 mL/min), the elimination half-life of famotidine may exceed 20 hours and adjustment of dose or dosing intervals for patients with moderate or severe renal insufficiency may be necessary (refer to section 4.2 and 4.4).

Renal excretion increases in a dose-dependent linear fashion, but the AUC and  $C_{max}$  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 famotidine. However, in elderly patients with decreased renal function, the clearance of the drug may be decreased (refer to section 4.2 and 4.4).

### **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 IV 20 mg dose, or multiple (once daily for 7 days) oral 40 mg doses.

### **5.3. Preclinical safety data**

Refer to section 4.6.

## **6. PHARMACEUTICAL PARTICULARS**

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### **6.1. List of excipients**

Pepzan tablet contains magnesium stearate, microcrystalline cellulose, Opadry buff OY-3682, pregelatinised maize starch, purified talc.

## **6.2. Incompatibilities**

Not applicable.

## **6.3. Shelf life**

36 months

## **6.4. Special precautions for storage**

Store at or below 30°C.

## **6.5. Nature and contents of container**

**Pepzan 20 mg tablet:** blister pack with 30, 120 tablets and plastic bottle pack with 30 tablets

**Pepzan 40 mg tablet:** blister and plastic bottle packs with 30 tablets

Not all strength and pack sizes may be marketed.

## **6.6. Special precautions for disposal and other handling**

Any unused medicine or waste material should be disposed of in accordance with local requirements.

# **7. MEDICINE SCHEDULE**

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Prescription medicine

# **8. SPONSOR**

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Douglas Pharmaceuticals Ltd

P O Box 45 027

Auckland 0651

New Zealand

Phone: (09) 835 0660

# **9. DATE OF FIRST APPROVAL**

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14 March 1991

# **10. DATE OF REVISION OF THE TEXT**

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11 February 2019

Summary table of changes



<b>Section Changed</b>	<b>Summary of new information</b>
All	SPC format