

# RATIDINE

## Ampoule & Tablets

### Composition

#### Ratidine 50 mg Injection

Each ampoule contains Ranitidine (as hydrochloride) 50 mg.

#### Ratidine 150 Tablets

Each tablet contains Ranitidine (as hydrochloride) 150 mg.

### Action

Ranitidine is a specific, rapidly acting histamine H<sub>2</sub>-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Ranitidine has a relatively long duration of action and so a single 150 mg dose effectively suppresses gastric acid secretion for twelve hours. Clinical evidence has shown that ranitidine combined with amoxicillin and metronidazole eradicates *Helicobacter pylori* in approximately 90% of patients. This combination therapy has been shown to significantly reduce duodenal ulcer recurrence. *Helicobacter pylori* infect about 95% of patients with duodenal ulcer and 80% of patients with gastric ulcer.

### Pharmacokinetics

#### Tablet

The bioavailability of ranitidine is consistently about 50%. Peak concentrations in plasma, normally in the range 300-550 ng/mL, occur 2-3 hours after oral administration of a 150 mg dose. Concentrations of ranitidine in plasma are proportional to dose up to and including 300 mg.

Ranitidine is not extensively metabolised. Elimination of the drug is primarily by tubular secretion. The elimination half-life is 2-3 hours. 60-70% of an oral dose is excreted in urine and 26% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 35% of the oral dose was eliminated unchanged. The metabolism of ranitidine is similar after both oral and intravenous dosing; about 6% of the dose being excreted in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1-2% as the furoic acid analogue.

#### Injection

Absorption of ranitidine after intramuscular injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration. Ranitidine is not extensively metabolised. Elimination of the drug is primarily by tubular secretion. The elimination half-life is 2-3 hours. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose was eliminated unchanged.

### Indications

Ranitidine is indicated for the treatment of the following conditions:

- Duodenal ulcer and benign gastric ulcer.
- Peptic ulcers associated with the use of non-steroidal anti-inflammatory agents (NSAID's).
- Post-operative ulcer.
- Zollinger-Ellison syndrome.
- Esophageal reflux disease.

Ranitidine is also indicated for conditions where reduction of gastric secretion and acid output is desirable, such as:

- Prophylaxis of gastrointestinal hemorrhage from stress ulceration in seriously ill patients.
- Prophylaxis of recurrent hemorrhage in patients with bleeding peptic ulcers.

Before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labor.

## **Contraindications**

Known hypersensitivity to the drug.

## **Warnings**

### **Pregnancy**

*Category B*

There are no adequate and well-controlled studies in pregnant women. This drug should be used during pregnancy only if clearly needed.

### **Nursing Mothers**

Ranitidine is secreted in human milk. Caution should be exercised when Ranitidine is administered to a nursing mother.

### **Paediatric Use**

Safety and efficacy for the use of Ranitidine in children have not been established.

### **Elderly Use**

Ulcer healing rates in elderly patients (65-82 years of age) were no different from those in younger age groups. The incidence rates for adverse events and laboratory abnormalities were also no different from those seen in other age groups.

## **Adverse Reactions**

The following have been reported as events in clinical trials or in the routine management of patients treated with Ranitidine. The relationship to Ranitidine therapy has been unclear in many cases.

### **Central Nervous System**

Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Headache, sometimes severe, has been reported, and seems to be related to Ranitidine administration. Rare cases of reversible mental confusion, agitation, depression and hallucinations have been reported, predominantly in severely ill elderly patients.

Other reported adverse reactions include rare cases of reversible blurred vision suggestive of a change in accommodation and rare incidences of reversible involuntary motor disturbances.

### **Cardiovascular**

As with other H<sub>2</sub>-receptor antagonists, there have been rare reports of arrhythmias such as tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

### **Gastrointestinal**

Constipation, diarrhea, nausea, vomiting, abdominal discomfort/pain and rare reports of pancreatitis.

### **Hepatic**

There have been occasional reports of hepatitis (hepatocellular, hepatocanalicular or mixed), with or without jaundice, associated with the use of Ranitidine. These were usually reversible. In such circumstances, Ranitidine must be immediately discontinued.

### **Musculoskeletal**

Rare reports of arthralgias.

### **Hematopoietic**

Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.

### **Dermatological**

Rash, including rare cases suggestive of mild erythema multiforme and, rarely, alopecia.

### **Other**

Rare cases of hypersensitivity reactions (including bronchospasm, fever, rash, eosinophilia, anaphylaxis, angioneurotic edema) and small increases in serum creatinine have occasionally occurred after a single dose.

### **Precautions**

Treatment with H<sub>2</sub>-receptor antagonists may mask symptoms associated with carcinoma of the stomach and may therefore delay diagnosis of the condition.

Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Ranitidine is instituted, since symptomatic response to Ranitidine therapy does not preclude the presence of gastric malignancy. Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with severe renal impairment. Accordingly, it is recommended in such patients that Ranitidine be administered in doses of 25 mg (1 ml of Ranitidine injection). Rapid administration of Ranitidine injection may rarely cause bradycardia similar to that induced by reflex vagal hypertonia and may exceptionally reduce ventricular rate and cardiac output, usually in association with myocardial impairment due to other causes.

It has been reported that use of higher than recommended doses of intravenous H<sub>2</sub>-antagonists has been associated with rises in liver enzymes when treatment has been extended beyond 5 days. Caution should be observed in patients with hepatic dysfunction since Ranitidine is metabolized in the liver.

### **Drug Interactions**

Although Ranitidine has been reported to bind weakly to cytochrome P450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P450 linked oxygenase enzymes in the liver. Accordingly, Ranitidine does not usually potentiate the actions of drugs which are inactivated by these enzymes (e.g. diazepam, lidocaine, phenytoin, propranolol, metoprolol, and theophylline), with the exception of some isolated cases that have been reported.

#### *Ranitidine/ Warfarin*

Increased or decreased prothrombin times have been reported during concurrent use of Ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of Ranitidine up to 400 mg/day, no interaction occurred; Ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of Ranitidine higher than 400 mg/day has not been investigated.

#### *Ranitidine/ Propantheline*

Propantheline slightly delays and increases peak blood levels of Ranitidine, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of Ranitidine.

#### *Ranitidine/ Procainamide*

Concomitant administration may result in increased Procainamide concentrations, because of decreased renal clearance of Procainamide following competition with Ranitidine for active tubular secretion. The dose of Procainamide should therefore be adjusted accordingly.

#### *Ranitidine/ Antacids*

Simultaneous administration of H<sub>2</sub>-receptor antagonists and antacids is not recommended, since antacids have been reported to interfere with the absorption of the H<sub>2</sub>-receptor antagonist. However, concomitant use of Ranitidine and antacids may be indicated for the relief of pain, in which case patients should be advised to allow a lapse of at least 2 hours between taking this drug and antacids.

#### *Ranitidine/ Ketoconazole*

Concomitant administration of ketoconazole with H<sub>2</sub>-receptor antagonists may result in a marked reduction in the absorption of ketoconazole. Therefore, patients should be advised to take H<sub>2</sub>-receptor antagonists at least 2 hours after ketoconazole.

#### **Diagnostic Interference**

False-positive tests for urine protein with Multistix may occur during Ranitidine therapy. Therefore testing with sulfosalicylic acid is recommended.

H<sub>2</sub>-receptor antagonists may antagonize the effect of pentagastrin and histamine in the evaluation of gastric acid secretory function. Therefore, administration of H<sub>2</sub>-receptor antagonists is not recommended during the 24 hours preceding the test.

#### **Dosage and Administration**

The use of Ranitidine injection in children has not been evaluated.

#### **Duodenal Ulcer and Benign Gastric Ulcer**

150 mg twice daily, morning and evening. Alternatively, a single dose of 300 mg may be taken at bedtime.

In most cases, healing occurs within 4 weeks. However, a further 4 weeks of treatment may be needed in patients whose ulcers have not fully healed after the initial course of therapy.

In duodenal ulcers, 300 mg administered twice daily for 4 weeks resulted in healing rates higher than those obtained at 4 weeks using 150 mg twice daily or 300 mg once daily at bedtime. The increased dose has not been associated with an increased incidence of adverse effects.

Maintenance treatment is recommended for patients who have responded to short-term therapy, particularly those with a history of recurrent ulcer. The recommended maintenance dosage is 150 mg at bedtime.

#### **Peptic Ulcers associated with the use of NSAID's**

The recommended dosage is the same as in duodenal and benign gastric ulcer. Duration of 8 weeks treatment may be necessary.

#### **Post-Operative Ulcer**

150 mg twice daily, morning and evening. Alternatively, a single dose of 300 mg may be taken at bedtime. In most cases, healing occurs within 4 weeks. However, a further 4 weeks of treatment may be needed in patients whose ulcers have not fully healed after the initial course of therapy.

#### **Zollinger-Ellison Syndrome**

The initial dosage is 150 mg 3 times daily, which may be increased as necessary. Dosages up to 6 grams per day have been administered and have been well tolerated.

#### **Esophageal Reflux Disease**

150 mg twice daily, morning and evening. Alternatively, a single dose of 300 mg may be taken at bedtime. Duration of treatment is usually up to 8 weeks.

#### **Other Indications**

In the prophylaxis of gastrointestinal hemorrhage from stress ulceration in seriously ill patients or the prophylaxis of recurrent hemorrhage in patients with bleeding peptic ulcers, the recommended dosage is Ranitidine injection 50 mg as a slow intravenous injection followed by a continuous intravenous infusion of 0.125-0.250 mg/kg/hr, or 150 mg orally twice daily, morning and evening.

In patients considered at risk of acid aspiration (Mendelson's syndrome), Ranitidine injection 50 mg may be given intravenously or by slow intravenous injection 45 to 60 minutes before induction of general anesthesia, or alternatively 150 mg may be administered 2 hours before induction of general anesthesia and, preferably also, 150 mg the previous evening.

In obstetric patients at commencement of labor, an oral dose of 150 mg may be administered, followed by 150 mg at 6-hourly intervals. It is recommended that since gastric emptying and drug absorption are delayed during labor, any patient requiring emergency general anaesthesia should be given, in addition, a non-particulate antacid (e.g. sodium citrate) prior to induction of anaesthesia. The usual precautions to avoid acid aspiration should also be taken.

### **Pharmaceutical Precautions**

Ranitidine tablets should be stored below 30 C°. The injection should be stored below 25 C°, protected from light. The injection should not be autoclaved.

Ranitidine injection is compatible with the following intravenous infusion fluids:

0.9% Sodium Chloride BP

5% Dextrose BP

0.18% Sodium Chloride and 4% Dextrose BP

4.2% Sodium Bicarbonate BP

Hartmann's Solution

### **Over Dosage**

#### **Manifestations**

Experience with over dosage of Ranitidine has been limited.

Reported acute ingestions of up to 18 grams orally have been associated with transient adverse effects similar to those encountered in normal clinical experience. In addition, abnormalities of gait and hypotension have been reported.

#### **Treatment**

The usual measures to remove unabsorbed material from the gastrointestinal tract, clinical monitoring, and supportive therapy should be employed. The drug may be removed from the plasma by haemodialysis.

### **Presentation**

#### **Ranitidine 50 mg Injection**

Box of 5 ampoules for intramuscular and intravenous injection.

#### **Ranitidine 150 mg Tablets**

Box of 20 tablets.