

# ZANTAC™

## Ranitidine hydrochloride

### QUALITATIVE AND QUANTITATIVE COMPOSITION

For all presentations, ranitidine is present as the hydrochloride salt.

*Syrup:* Ranitidine 150 mg in 10 ml.

*Tablets:* Ranitidine 150 mg or 300 mg.

*Injection:* Ranitidine 50 mg in 2 ml aqueous solution (25 mg/ml).

### PHARMACEUTICAL FORM

#### *Oral Formulations*

Syrup.

Tablets: film-coated.

#### *Parenteral Formulation*

Injection.

### CLINICAL PARTICULARS

#### Indications

##### *Oral formulations:*

- Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
- Post-operative ulcer.
- Reflux oesophagitis.
- Zollinger-Ellison Syndrome.
- Chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.
- Prophylaxis of stress ulceration in seriously ill patients.
- Prophylaxis of recurrent haemorrhage from peptic ulcer.
- Prophylaxis of Mendelson's syndrome.

***Injection:***

- Duodenal ulcer.
- Benign gastric ulcer.
- Post-operative ulcer.
- Reflux oesophagitis.
- Zollinger-Ellison Syndrome.
- Prophylaxis of stress ulceration in seriously ill.
- Prophylaxis of recurrent haemorrhage from peptic ulcer.
- Prophylaxis of Mendelson's syndrome.

**Dosage and Administration****General Information:**

Syrup:

ZANTAC syrup contains approximately 7.5% w/v ethanol (alcohol), i.e. up to 405 mg per 5 ml spoonful (approximately a teaspoonful) which is equivalent to about 11 ml of beer or 5 ml of wine.

**Populations**

- **Adults/Adolescents (12 years and over)**

***Oral Formulations:*****DUODENAL ULCER AND BENIGN GASTRIC ULCER****Acute treatment**

The standard dosage regimen for duodenal or benign gastric ulcer is 150 mg twice daily or 300 mg once nightly. In most cases of duodenal ulcer or benign gastric ulcer healing occurs within 4 weeks. Healing usually occurs after a further 4 weeks in those not fully healed after the initial 4 weeks.

In duodenal ulcer 300 mg twice daily for 4 weeks results in healing rates which are higher than those at 4 weeks with ZANTAC 150 mg twice daily or 300 mg once nightly. The increased dose has not been associated with an increased incidence of unwanted effects.

### **Long-term management**

For the long-term management of duodenal or benign gastric ulcer the usual dosage regimen is 150 mg once nightly.

Smoking is associated with a higher rate of duodenal ulcer relapse, and such patients should be advised to stop smoking. In those who fail to comply with such advice a dose of 300 mg once nightly provides additional therapeutic benefit over the 150 mg dosage regimen.

### **POST-OPERATIVE ULCER**

The standard dosage regimen for post-operative ulcer is 150 mg twice daily.

Most cases heal within 4 weeks. Those not fully healed after the initial four weeks usually do so after a further 4 weeks.

### **GASTRO-OESOPHAGEAL REFLUX DISEASE**

#### **Acute treatment**

In mild to moderate reflux oesophagitis, 150 mg twice daily or 300 mg once nightly is administered for up to a period of 8 weeks. In patients with severe oesophagitis, the dosage of ZANTAC may be increased to 150 mg 4 times daily for up to 8 weeks.

### **ZOLLINGER-ELLISON SYNDROME**

The initial dosage regimen for Zollinger-Ellison syndrome is 150 mg 3 times daily, but this may be increased as necessary. Doses up to 6 g per day have been well tolerated.

### **CHRONIC EPISODIC DYSPEPSIA**

The standard dosage regimen for patients with chronic episodic dyspepsia is 150 mg twice daily for up to 6 weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

### **PROPHYLAXIS OF MENDELSON'S SYNDROME**

150 mg 2 hours before anaesthesia, and preferably 150 mg the previous evening. Alternatively, the injection is also available. In obstetric patients in labour 150 mg every 6 hours, but if general anaesthesia is required it is recommended that a non-particulate antacid (e.g. sodium citrate) be given in addition.

### **PROPHYLAXIS OF HAEMORRHAGE FROM STRESS ULCERATION IN SERIOUSLY ILL PATIENTS OR PROPHYLAXIS OF RECURRENT HAEMORRHAGE IN PATIENTS BLEEDING FROM PEPTIC ULCERATION**

150 mg twice daily may be substituted for the injection once oral feeding commences.

**Injection:**

ZANTAC Injection may be given as:

- a slow (over 2 minutes) intravenous (i.v.) injection of 50 mg, diluted to a volume of 20 ml, every 6 to 8 hours.
- an intermittent i.v. infusion at 25 mg/h for 2 hours, repeated at 6 to 8 hour intervals.
- an intramuscular (i.m.) injection of 50 mg every 6 to 8 hours.

**PROPHYLAXIS OF MENDELSON'S SYNDROME**

For prophylaxis of Mendelson's syndrome 50 mg by i.m. or slow i.v. injection 45 to 60 minutes before induction of general anaesthesia.

**PROPHYLAXIS OF HAEMORRHAGE FROM STRESS ULCERATION IN SERIOUSLY ILL PATIENTS OR PROPHYLAXIS OF RECURRENT HAEMORRHAGE IN PATIENTS BLEEDING FROM PEPTIC ULCERATION**

In the prophylaxis of haemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent haemorrhage in patients bleeding from peptic ulceration parenteral administration may be continued until oral feeding commences. Patients considered to be still at risk may then be treated with ZANTAC tablets 150 mg twice daily.

In the prophylaxis of upper gastrointestinal haemorrhage from stress ulceration in seriously ill patients, a priming dose of 50 mg as a slow i.v. injection followed by a continuous i.v. infusion of 0.125-0.250 mg/kg/h may be preferred.

- **Children (up to 11 years)**

The recommended oral dose for the treatment of peptic ulcer in children is 4 mg/kg/day to 8 mg/kg/day administered as two divided doses to a maximum of 300 mg ZANTAC per day.

Use of ZANTAC injection in children has not been evaluated.

- **Patients over 50 years of age**

*(see Pharmacokinetics, Special Patient Populations, Patients over 50 years of age)*

- **Renal Impairment**

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50 ml/min). It is recommended that the daily dose of oral ZANTAC in such patients should be 150 mg, and that ZANTAC injection be administered in doses of 25 mg.

## **Contraindications**

ZANTAC products are contraindicated in patients known to have hypersensitivity to any component of the preparation.

## **Warnings and Precautions**

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer and patients of middle age and over with new or recently changed dyspeptic symptoms, as treatment with ZANTAC may mask symptoms of gastric carcinoma.

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with renal impairment.

The dosage should be adjusted as detailed above under *Dosage and Administration in Renal Impairment*.

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. ZANTAC should therefore be avoided in patients with a history of acute porphyria.

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with oral ZANTAC is recommended, especially in the elderly and in those with a history of peptic ulcer.

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 H<sub>2</sub> - receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07 - 2.48).

Bradycardia in association with rapid administration of ZANTAC injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded.

The use of higher than recommended doses of i.v. H<sub>2</sub>- antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

## **Interactions**

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1) Inhibition of cytochrome P450-linked mixed function oxygenase system:

Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2) Competition for renal tubular secretion:

Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs. Although this interaction is unlikely to be clinically relevant at usual ranitidine doses, it may be prudent to monitor for procainamide toxicity when administered with oral ranitidine at a dose exceeding 300 mg per day.

3) Alteration of gastric pH:

The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitinib).

There is no evidence of an interaction between oral ranitidine and amoxicillin and metronidazole.

If high doses (2 g) of sucralfate are co-administered with oral ranitidine the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

## **Pregnancy and Lactation**

### **Fertility**

There are no data on the effects of ranitidine on human fertility. There were no effects on male and female fertility in animal studies (*see Pre-Clinical Safety Data*).

### **Pregnancy and lactation**

Ranitidine crosses the placenta and is excreted in breast milk. Like other drugs ZANTAC should only be used during pregnancy or during breast-feeding if considered essential.

### **Effects on Ability to Drive and Use Machines**

None reported.

## **Adverse Reactions**

The following convention has been utilised for the classification of undesirable effects: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1000$ ), very rare ( $< 1/10,000$ ). Adverse event frequencies have been estimated from spontaneous reports from post-marketing data.

### **Blood & Lymphatic System Disorders**

Very Rare: Blood count changes (leucopenia, thrombocytopenia). These are usually reversible. Agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia.

### **Immune System Disorders**

Rare: Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension and chest pain).

Very Rare: Anaphylactic shock.

These events have been reported after a single dose.

### **Psychiatric Disorders**

Very Rare: Reversible mental confusion, depression and hallucinations.

These have been reported predominantly in severely ill and elderly patients.

### **Nervous System Disorders**

Very Rare: Headache (sometimes severe), dizziness and reversible involuntary movement disorders.

### **Eye Disorders**

Very Rare: Reversible blurred vision.

There have been reports of blurred vision, which is suggestive of a change in accommodation.

### **Cardiac Disorders**

Very Rare: As with other H<sub>2</sub> - receptor antagonists bradycardia, A-V block and, with the injection only, asystole.

### **Vascular Disorders**

Very Rare: Vasculitis.

### **Gastrointestinal Disorders**

Very Rare: Acute pancreatitis, diarrhoea.

### **Hepatobiliary Disorders**

- Rare: Transient and reversible changes in liver function tests.
- Very Rare: Hepatitis (hepatocellular, hepatocanalicular or mixed) with or without jaundice, these were usually reversible.

### **Skin and Subcutaneous Tissue Disorders**

- Rare: Skin rash.
- Very Rare: Erythema multiforme, alopecia.

### **Musculoskeletal and Connective Tissue Disorders**

- Very Rare: Musculoskeletal symptoms such as arthralgia and myalgia.

### **Renal and Urinary Disorders**

- Very rare: Acute interstitial nephritis.

### **Reproductive System and Breast Disorders**

- Very Rare: Reversible impotence, breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea).

### **Overdose**

Ranitidine is very specific in action and no particular problems are expected following overdose with *ZANTAC* formulations. Symptomatic and supportive therapy should be given as appropriate.

Syrup:

*ZANTAC* syrup contains approximately 7.5% w/v ethanol (alcohol), i.e. up to 405 mg per 5 ml spoonful (approximately a teaspoonful) which is equivalent to about 11 ml of beer or 5 ml of wine. This should be taken into account in children, pregnant or lactating women, or high risk groups (alcoholism, liver disease, epilepsy, brain injury or disease). It may modify or increase the effect of other medicines.

### **Pharmacodynamics**

#### ***Mechanism of 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.

#### ***Pharmacodynamic Effects***

Ranitidine has a relatively long duration of action and so a single 150 mg oral dose effectively suppresses gastric acid secretion for 12 hours.



## **Pharmacokinetics**

### ***Absorption***

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/ml) occurred after 1-3 hours. Two distinct peaks or a plateau in the absorption phase result from reabsorption of drug excreted into the intestine. The absolute bioavailability of ranitidine is 50-60%, and plasma concentrations increase proportionally with increasing dose up to 300 mg.

Absorption of ranitidine after i.m. injection is rapid and peak plasma concentrations are usually achieved within 15 minutes of administration.

### ***Distribution***

Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

### ***Metabolism***

Ranitidine is not extensively metabolised. The fraction of the dose recovered as metabolites is similar after both oral and i.v. dosing; and includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1 to 2% as the furoic acid analogue.

### ***Elimination***

Plasma concentrations decline bi-exponentially, with a terminal half-life of 2-3 hours. The major route of elimination is renal. After i.v. administration of 150 mg 3H-ranitidine, 98% of the dose was recovered, including 5% in faeces and 93% in urine, of which 70% was unchanged parent drug. After oral administration of 150 mg 3H-ranitidine, 96% of the dose was recovered, 26% in faeces and 70% in urine of which 35% was unchanged parent drug. Less than 3% of the dose is excreted in bile. Renal clearance is approximately 500 mL/ min, which exceeds glomerular filtration indicating net renal tubular secretion.

### ***Special Patient Populations***

- **Patients over 50 years of age**

In patients over 50 years of age, half-life is prolonged (3-4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

## **Pre-Clinical Safety Data**

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development.

## **PHARMACEUTICAL PARTICULARS**

### **Incompatibilities**

Dilution of *ZANTAC* syrup with Syrup BP or sorbitol solution is not recommended as this may result in precipitation. *ZANTAC* syrup should not be diluted or admixed with other liquid preparations.

For Injection information, see *Instructions for Use/Handling*.

### **Special Precautions for Storage**

*ZANTAC* syrup should be stored below 25°C.

*ZANTAC* film-coated tablets should be stored at a temperature below 30°C.

### ***Injection:***

Store below 25°C. Protect from light.

*ZANTAC* injection should not be autoclaved.

### **Instructions for Use/Handling**

*ZANTAC* injection is a clear, colourless to pale yellow liquid.

*ZANTAC* injection is compatible with the following i.v. infusion fluids:

- 0.9% sodium chloride
- 5% dextrose
- 0.18% sodium chloride and 4% dextrose
- 4.2% sodium bicarbonate
- Hartmann's solution.

Unused admixtures should be discarded 24 hours after preparation.

Although compatibility studies have only been undertaken in polyvinyl chloride infusion bags (in glass for sodium bicarbonate) and polyvinyl chloride administration sets, it is considered that adequate stability would be conferred by the use of a polyethylene infusion bag.

Not all presentations are available in every country.

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