

Prescribing Information/Insert

ZANTAC™

QUALITATIVE AND QUANTITATIVE COMPOSITION

Zantac 150 mg: Each tablet contains 150 mg of Ranitidine hydrochloride BP.

PHARMACEUTICAL FORM

Zantac 150 mg: Film-coated tablet.

CLINICAL INFORMATION

Indications

Adults/Adolescents (12 years and over)

- Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
- Prevention of non-steroidal anti-inflammatory drug (NSAID) (including aspirin) associated duodenal ulcers, especially in patients with a history of peptic ulcer disease.
- Duodenal ulcer associated with *Helicobacter pylori* infection.
- Post-operative ulcer.
- Reflux oesophagitis.
- Symptom relief in gastro-oesophageal reflux disease.
- 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.

Children/Infants (1 month to 11 years)

- Treatment of peptic ulcer
- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptom relief of gastro-oesophageal reflux disease

Dosage and Administration

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.

NSAID ASSOCIATED PEPTIC ULCERATION

Acute treatment

In ulcers following non-steroidal anti-inflammatory drug therapy, or associated with continued non-steroidal anti-inflammatory drugs, 8 to 12 weeks treatment may be necessary with 150 mg twice daily or 300 mg once nightly.

Prophylaxis

For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers ZANTAC 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

DUODENAL ULCER ASSOCIATED WITH *HELICOBACTER PYLORI* INFECTION

ZANTAC 300 mg once nightly or 150 mg twice daily may be given with oral amoxicillin 750 mg 3 times daily and metronidazole 500 mg 3 times daily for 2 weeks. Therapy with ZANTAC only should continue for a further 2 weeks. This dose regimen significantly reduces the frequency of duodenal ulcer recurrence.

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 4 weeks usually do so after a further 4 weeks.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Acute treatment

In reflux oesophagitis 150 mg twice daily or 300 mg once nightly is administered for up to a period of 8, or if necessary, 12 weeks.

In patients with moderate to severe oesophagitis, the dosage of ZANTAC may be increased to 150 mg 4 times daily for up to 12 weeks.

Long-term management

For the long-term management of reflux oesophagitis, the recommended adult oral dose is 150 mg twice daily.

Symptom relief

For the relief of symptoms associated with oesophageal acid reflux, the recommended regimen is 150 mg twice daily for 2 weeks. This regimen may be continued for a further 2 weeks in those patients in whom the initial response is inadequate.

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.

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/Infants (1 month to 11 years) (see Pharmacokinetics, Special Patient Populations, Children/Infants)**

Oral formulations:

PEPTIC ULCER

Acute treatment

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. For those patients with incomplete healing, another 4 weeks of therapy is indicated, as healing usually occurs within 8 weeks of treatment.

GASTRO-OESOPHAGEAL REFLUX

The recommended oral dose for the treatment of gastro-oesophageal reflux in children is 5 mg/kg/day to 10 mg/kg/day administered as two divided doses to a maximum of 600 mg ZANTAC per day.

PEPTIC ULCER acute treatment AND GASTRO-OESOPHAGEAL REFLUX

The recommended i.v. dose for the treatment for peptic ulcer and gastro-oesophageal reflux in children is 2 mg/kg/day to 4 mg/kg/day administered as two to four divided doses. This recommendation is derived from adult clinical studies and pharmacokinetic data in paediatric patients.

PROPHYLAXIS OF STRESS ULCERATION IN SERIOUSLY ILL PATIENTS

The recommended i.v. dose for prophylaxis of stress ulceration in seriously ill patients is 2 mg/kg/day to 6 mg/kg/day administered as two to four divided doses. Alternatively, ZANTAC may be administered for prophylaxis of stress ulceration in seriously ill patients by continuous infusion.

• Neonates (under 1 month) (see Pharmacokinetics, Special Patient Populations, Neonates)

Safety and efficacy in neonates has not been established.

• 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 H₂-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. H₂- 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.

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, delavirdine, 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.

Ability to drive and use machine

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 H₂ 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)

Overdosage

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.

Pharmacodynamics

Mechanism of Action

Ranitidine is a specific, rapidly acting histamine H₂-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.

Clinical evidence has shown that oral 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* infects about 95% of patients with duodenal ulcer and 80% of patients with gastric ulcer.

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 desmethyl ranitidine 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

Children/Infants (1 month to 11 years)

Limited pharmacokinetic data have shown that the half-life (2-3 hours) and plasma clearance (9-13 ml/min/kg) in children 1 month and above are similar to those for healthy adults receiving oral ranitidine.

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

List of Excipients

Microcrystalline cellulose (Avicel PH 102), Magnesium stearate, Opadry white OY-S-7322 (Composition : Hypromellose (viscosity 5-6), TiO₂, Methocel)

Shelf-Life

24 months.

Storage:

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

Nature and Content of Container

10 x 10's in aluminium blisters.

Incompatibilities

There are no relevant data available.

Use and Handling

No special requirements

Version Number: GDS 44/IPI 10

Version Date: 11 February 2013

Manufactured by

GlaxoSmithKline Bangladesh Limited,
Fouzderhat Industrial Area, Chittagong

