ZANTAC™ Tablets

To the Medical and Pharmaceutical Professions.

Presentations

Not all presentations are registered in every country.
Zantac Tablets 150 mg: Each tablet contains ranitidine 150 mg (as the hydrochloride).
Zantac Tablets 300 mg: Each tablet contains ranitidine 300 mg (as the hydrochloride).

Indications

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Duodenal ulcer and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
Prevention of non-steroidal anti-inflammatory drug (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.

Dosage and Administration

Dosage in adults:

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 nocte. 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 ranitidine 150 mg twice daily or 300 mg nocte. 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 nocte.
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 nocte 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, 8-12 weeks treatment may be necessary with 150 mg twice daily or 300 mg nocte.
Prophylaxis:
For the prevention of non-steroidal anti-inflammatory drug associated duodenal ulcers ranitidine 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 at bedtime or 150 mg twice daily may be given with oral amoxycillin 750 mg three times daily and metronidazole 500 mg three times daily for two weeks. Therapy with Zantac only should continue for a further two 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 reflux oesophagitis:
In reflux oesophagitis 150 mg twice daily or 300 mg nocte is administered for up to a period of 8, or if necessary, 12 weeks.
In patients with moderate to severe oesophagitis, the dosage of ranitidine may be increased to 150 mg four times daily for up to 12 weeks.
Long-term management of reflux oesophagitis:
For the long-term management of reflux oesophagitis the recommended adult oral dose is 150 mg twice daily.
Symptom relief in gastro-oesophageal reflux disease:
For the relief of symptoms associated with oesophageal acid reflux, the recommended regimen is 150 mg twice daily for two weeks. This regimen may be continued for a further two 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 three times daily, but this may be increased as necessary. Doses up to 6 grams 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 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:
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.

Dosage in children:

The recommended oral dose for the treatment of peptic ulcer in children is 2 mg/kg to 4 mg/kg twice daily to a maximum of 300 mg ranitidine per day.

Renal Impairment:

Accumulation of ranitidine with resulting elevated plasma concentrations will occur in patients with severe renal impairment (creatinine clearance less than 50 ml/min). It is recommended that the daily dose of ranitidine in such patients should be 150 mg. In patients undergoing chronic ambulatory peritoneal dialysis or chronic haemodialysis, ranitidine (150 mg) should be taken immediately after dialysis.

Contra-indications

Zantac is contra-indicated in patients known to have hypersensitivity to any component of the preparation.

Precautions and Warnings

Malignancy:

The possibility of malignancy should be excluded before commencement of therapy in patients with gastric ulcer (and if indications include dyspepsia; patients of middle age and over with new or recently changed dyspeptic symptoms) as treatment with ranitidine may mask symptoms of gastric carcinoma.

Renal Disease:

Ranitidine is excreted via the kidney and so plasma levels of the drug are increased in patients with severe renal impairment.
The dosage should be adjusted as detailed above under Dosage and Administration, Renal Impairment.
Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ranitidine is recommended, especially in the elderly and in those with a history of peptic ulcer.

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

Drug Interactions

Ranitidine, at blood levels produced by standard recommended doses, does not inhibit the hepatic cytochrome P 450-linked mixed function oxygenase system. Accordingly, ranitidine in usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme; these include diazepam, lignocaine, phenytoin, propranolol, theophylline and warfarin. There is no evidence of an interaction between ranitidine and amoxycillin and metronidazole.

If high doses (2 g) of sucralfate are co-administered with 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

Ranitidine crosses the placenta and is excreted in human breast milk.

Like other drugs it should only be used during pregnancy and nursing if considered essential.

Adverse Reactions

The following convention has been utilised for the classification of undesirable effects: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10,000, <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_2 receptor antagonists bradycardia and A-V Block.

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 in men.

Overdosage

Ranitidine is very specific in action and no particular problems are expected following overdosage with Zantac Tablets.

Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

Pharmacodynamic Properties

Mode of action:

Zantac is a specific, rapidly acting histamine H_2-antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion. Zantac 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 amoxycillin 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.

Pharmacokinetic Properties

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.

In balance studies with 150 mg ^{3}H-ranitidine 93% of an intravenous dose was excreted in urine and 5% in faeces; 60-70% of an oral dose was excreted in urine and 26% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose and 35% of the oral dose were 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.

Pharmaceutical Precautions and Recommendations

Do not store above 30°C.

List of Excipients

Tablet core:
Microcrystalline cellulose.
Croscarmellose sodium (300 mg tablet only).
Magnesium stearate.

Film coat:
Methyhydroxypropylcellulose E-464.
Titanium dioxide (E171).
Triacetin.

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