Zantac™ Film – Coated Tablets

NAME OF THE MEDICINAL PRODUCT

Zantac 150 mg film-coated tablets
Zantac 300 mg film-coated tablets

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 150 mg or 300 mg of ranitidine in the form of ranitidine hydrochloride. For a full list of excipients, see section"List Of Excipients"

PHARMACEUTICAL FORM

Zantac 150 mg film-coated tablets are biconvex, film-coated and white in colour. Each tablet contains ranitidine base 150 mg for oral administration. Each tablet is engraved with "GX EC2" on one side.

Zantac 300 mg film-coated tablets are capsule-shaped, film-coated and white in colour. Each tablet contains ranitidine base 300 mg for oral administration. Each tablet is engraved with "GX EC3" on one side.

CLINICAL PARTICULARS

Therapeutic indications for children (3 to 18 years)

- Short-term treatment of peptic ulcer
- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptomatic relief of gastro-oesophageal reflux disease.

Adults

- Duodenal ulcer
- Benign gastric ulcer
- Zollinger-Ellison syndrome
- Treatment of gastro-oesophageal haemorrhage with hypersecretion and prophylaxis of recurrent haemorrhage in patients with bleeding ulcer.
- Peptic oesophagitis and treatment of associated symptoms.
- Prophylaxis of gastrointestinal haemorrhage from stress ulceration in seriously ill patients.
- During to preoperative period, in patients at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

Before prescribing Zantac, the physician must ensure, through full assessment of the patient's medical history and use of appropriate diagnostic means, that the clinical picture can be matched to one of the indications.

Zantac must not be used to correct dyspepsia, gastritis, or any other minor disorder.

The possibility that the condition being treated is of a neoplastic nature, whereby the drug, upon relieving symptoms, may mask the developing clinical picture, should be excluded.

Posology and method of administration

Adults

For **active duodenal ulcer**, the standard dosage regimen is 150 mg twice daily orally (taken in the morning and at night). It is not necessary to time the dose in relation to meals. A single dose of 300 mg at night can be equally effective.

This course of treatment should be maintained in any event for 4 to 6 weeks, even if symptoms are relieved in less time, and may be discontinued earlier if there is objective evidence (e.g. fibroscopy) that the ulcer has healed.

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

For **active benign gastric ulcer**, the standard dosage regimen is 150 mg twice daily or 300 mg at night for 6 weeks.

In patients with **reflux oesophagitis**, the recommended course of treatment is either 150 mg twice daily or 300 mg at bedtime for up to 6-8 weeks, or 12 weeks if necessary. 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. For long-term treatment, the recommended oral dose is 150 mg twice daily. For the **treatment of associated symptoms**, an oral dosage regimen of 150 mg twice daily for 2 weeks is recommended; this can be continued for a further 2 weeks in patients in whom the initial symptomatic response was inadequate.

In patients with **Zollinger-Ellison syndrome**, the starting dose is 150 mg three times daily and this may be increased as necessary. Patients with this syndrome have been given doses up to 6 g/day.

For the **prevention of Mendelson's syndrome**, an oral dose of 150 mg can be given 2 hours before induction of general anaesthesia, and preferably also 150 mg the previous evening. Alternatively, 50 mg may be given by slow intramuscular or intravenous administration 45 to 60 minutes before anaesthesia. In obstetric patients at commencement of labour, a dose of 150 mg may be given followed by 150 mg at 6 hourly intervals. It is recommended that since gastric emptying and drug absorption are delayed during labour, any patient requiring emergency general anaesthesia before two hours have elapsed since taking the last tablet should be given a liquid antacid preparation (e.g. sodium citrate) prior to induction of anaesthesia. The usual precautions to avoid acid aspiration should also be taken.

Children from 3 to 11 years and over 30 kg in weight

See Pharmacokinetic - Special patient populations.

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 ranitidine per day for a duration of 4 weeks. For those patients with incomplete healing, another 4 weeks of therapy is indicated, as healing usually occurs after 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 dose of 600 mg (the maximum dose is more appropriate for heavier children or adolescents with severe symptoms).

Safety and efficacy in newborn patients has not been established.

Patients with renal insufficiency:

Accumulation of ranitidine with resulting elevated plasma concentrations can occur in patients with renal insufficiency (creatinine clearance less than 50 ml/min). It is recommended that the daily dose of ranitidine in such patients should start at 150 mg at night for 4-8 weeks. If the ulcer has not healed after this time and it is deemed necessary to continue treatment, the dose may be increased to 150 mg twice daily with caution.

To calculate the daily dose necessary for patients with renal insufficiency, in accordance with creatinine clearance, the following table shall be used:

Creatinine clearance (ml/minute)	Daily dose
>50	100% of the usual dose
10 – 50	75% of the usual dose
<10	50% of the usual dose

Use in elderly patients: the rate of healing of ulcers during clinical trials in patients older than 65 years is no different to that of younger patients.

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 Patients with Renal Insufficiency.*

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

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_2- receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk increase of 1.63 (95% CI, 1.07–2.48). 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.

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, delaviridine, gefitinib).

There is no evidence of an interaction between ranitidine and amoxicillin 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

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 Non-Clinical Information).*

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Pregnancy
Ranitidine crosses the placenta. Like other drugs Zantac should only be used during pregnancy if considered essential.
Lactation
Ranitidine is excreted in human breast milk. Like other drugs Zantac should only be used during breast-feeding if considered essential.
Ability to perform tasks that require judgement, motor or cognitive skills
None reported.
Adverse Reactions
The following convention has been utilised for the classification of undesirable effects: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥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_2 receptor antagonists bradycardia, A-V block and asystole (*injection only*).
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
Symptoms and Signs
Zantac is very specific in action and no particular problems are expected following overdose with Zantac formulations.
Treatment
Symptomatic and supportive therapy should be given as appropriate.
Clinical Pharmacology
Pharmacodynamics
ATC Code
Pharmacotherapeutic group: H2-receptor antagonists, ATC code: A02BA02.
Mechanism of Action
Ranitidine 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.
Pharmacodynamic Effects
Ranitidine has a relatively long duration of action and so a single 150 mg dose effectively suppresses gastric acid secretion for 12 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 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.
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 ^{3}H-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 ^{3}H-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 h) 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.
NON-CLINICAL INFORMATION
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 INFORMATION
List of excipients
Zantac 150 mg, film-coated tablets and Zantac 300 mg, film-coated tablets:
Microcrystalline cellulose
Magnesium stearate
Cross carmellose sodium (Zantac 300 mg, film-coated tablets)
Hypromellose (E464)
Titanium dioxide (E171)
Triacetin
Shelf-Life
As indicated on the outer packaging
Storage
Store at a temperature below 30°C.
Nature and Contents of Container
Zantac 150 mg, film-coated tablets: 28, 56 and 500 tablets containing 150 mg ranitidine (hydrochloride) in a double aluminium blister pack.
Zantac 300 mg, film-coated tablets: 14, 28 and 500 tablets containing 300 mg ranitidine (hydrochloride) in a double aluminium blister pack.
It is possible that only certain pack sizes may be marketed.
Manufactured By:
Manufactured by Glaxo Wellcome, S.A.*
Aranda de Duero, Spain
*Member of the GSK group of companies
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THIS IS A MEDICAMENT
Medicament is a product which affects your health and its consumption contrary to instructions is dangerous for you.
Follow strictly the doctor's prescription, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are the experts in medicines, their benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed.
- Do not repeat the same prescription without consulting your doctor.
- Keep all medicaments out of reach of children.

Council of Arab Health Ministers,
Union of Arab Pharmacists.

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