

DATA SHEET

ZANTAC® Syrup

Ranitidine Hydrochloride Syrup

Qualitative and quantitative composition

ZANTAC Syrup: Each 10mL contains ranitidine 150mg (as the hydrochloride).

Pharmaceutical form

Syrup.

Clinical particulars

Therapeutic Indications

ZANTAC Syrup is indicated for:

- the treatment of duodenal ulcer, and benign gastric ulcer, including that associated with non-steroidal anti-inflammatory agents.
- the prevention of non-steroidal anti-inflammatory agent (including aspirin) associated duodenal ulcers in patients with a history of duodenal ulceration proven by endoscopy.
- the treatment of post-operative ulcer
- the treatment of oesophageal reflux disease
- symptom relief in gastro-oesophageal reflux disease
- the treatment of Zollinger-Ellison syndrome
- the treatment of chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.

ZANTAC Syrup is also indicated for the following conditions where reduction of gastric secretion and acid output is desirable:

- the prophylaxis of upper gastrointestinal haemorrhage from stress ulceration in seriously ill patients.

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- the prophylaxis of recurrent haemorrhage 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 labour.

For appropriate cases ZANTAC Injection is also available (see ZANTAC Injection Data Sheet).

Posology and method of administration

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.

Adults

Duodenal Ulcer and Benign Gastric Ulcer

Acute Treatment

The usual dosage is 150mg twice daily, taken in the morning and evening. Alternatively, patients with duodenal or gastric ulceration may be treated with a single bedtime dose of 300mg. It is not necessary to time the dose in relation to meals.

In most cases of duodenal ulcer or benign gastric ulcer, healing occurs in 4 weeks. Healing usually occurs after a further 4 weeks of treatment in those patients whose ulcers have not fully healed after the initial course of therapy.

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

Long Term Management

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

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 300mg nocte provides additional therapeutic benefit over the 150mg dosage regimen.

NSAID Associated Peptic Ulceration

Acute Treatment

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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 150mg twice daily or 300mg nocte.

Prophylaxis

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

Postoperative Ulcer

The standard dosage regimen for postoperative ulcer is 150mg 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 the management of oesophageal reflux disease, the recommended course of treatment is either 150mg twice daily or 300mg at bedtime for up to 8 weeks.

In patients with moderate to severe oesophageal reflux disease, the dosage or ranitidine may be increased to 150mg four times daily for up to twelve weeks.

Long-term management of reflux oesophagitis

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

Symptom relief in gastro-oesophageal reflux disease

For the relief of symptoms associated with oesophageal acid reflux, the recommended regimen is 150mg 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

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

Chronic Episodic Dyspepsia

For patients with chronic episodic dyspepsia the recommended course of treatment is 150mg twice daily for up to 6 weeks. Anyone not responding or relapsing shortly afterwards should be investigated.

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Prophylaxis of Haemorrhage from Stress Ulceration in Seriously Ill Patients or the Prophylaxis of Recurrent Haemorrhage in Patients Bleeding from Peptic Ulceration

Treatment with ZANTAC syrup 150mg twice daily may be substituted for ZANTAC injection (see separate Data Sheet) once oral feeding commences in patients considered to be still at risk from these conditions.

Prophylaxis of Mendelson's Syndrome

In patients thought to be at risk of acid aspiration syndrome an oral dose of 150mg can be given 2 hours before induction of general anaesthesia, and preferably also 150mg orally the previous evening. Alternatively ZANTAC Injection for intravenous and intramuscular use is also available (see ZANTAC Injection Data Sheet).

In obstetric patients at commencement of labour, an oral dose of 150mg can be given followed by 150mg at 6 hourly intervals. It is recommended that since gastric emptying and medicine absorption are delayed during labour, 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.

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

Children

Experience with ZANTAC in children is limited and such use has not been fully evaluated in clinical studies. It has however been used successfully in children aged 8 to 18 years in doses up to 150mg twice daily.

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 ranitidine in such patients should be 150mg.

Contraindications

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

Special warnings and special precautions for use

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 in 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.

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 of 1.63 (95% CI, 1.07-2.48).

Interaction with other medicaments and other forms of interaction

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:

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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 (2g) 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.

Effects on the ability to drive and operate machinery

None reported.

Undesirable effects

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 not been established in many cases.

Blood & Lymphatic

Blood count changes (leucopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible. Rare cases of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or marrow aplasia have been reported.

Cardiovascular

As with other H₂ receptor antagonists, there have been rare reports of bradycardia and A-V Block. Rare cases of vasculitis have been reported.

Eye

There have been a few reports of reversible blurred vision suggestive of a change in accommodation.

Gastrointestinal

Very rare cases of diarrhoea have been reported.

Hepatobiliary tract & Pancreas

Transient and reversible changes in liver function-tests can occur. There have been occasional reports of hepatitis (hepatocellular, hepatocanalicular or

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mixed) with or without jaundice. These were usually reversible. Acute pancreatitis has been rarely reported.

Musculoskeletal

Musculoskeletal symptoms such as arthralgia and myalgia have been reported rarely.

Neurology/Psychiatry

Headache, sometimes severe and dizziness have been reported in a very small proportion of patients. Rare cases of reversible mental confusion, depression and hallucinations have been reported, predominantly in severely ill and elderly patients. In addition, reversible involuntary movement disorders have been reported rarely.

Non-site specific/Skin

Skin rash has been reported, including rare cases of erythema multiforme. Rare cases of alopecia have been reported.

Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension, anaphylactic shock, chest pain) have been seen rarely after a single dose.

Renal

Very rare cases of acute interstitial nephritis have been reported.

Reproductive System and Breast Disorders

Reversible impotence has been reported rarely. There have been a few reports of breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea).

Overdose

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

Symptomatic and supportive therapy should be given as appropriate.

Pharmacological properties

Pharmacodynamic properties

ZANTAC 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. ZANTAC has a relatively long duration of action and so a single 150mg 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 infects about 95% of patients with duodenal ulcer and 80% of patients with gastric ulcer.

Pharmacokinetic properties

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 550 ng/mL) occurred after 1 to 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 to 60%, and plasma concentrations increase proportionally with increasing dose up to 300mg. Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Ranitidine is not extensively metabolised. The fraction of the dose recovered as metabolites is similar after both oral and intravenous 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.

Plasma concentrations decline bi-exponentially, with a terminal half-life of 2 to 3 hours. The major route of elimination is renal. After intravenous administration of 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 to 4 hours) and clearance is reduced, consistent with 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.

Preclinical safety data

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No additional data of relevance.

Pharmaceutical particulars

List of excipients

Hydroxypropyl Methylcellulose 2906 or 2910.

Ethanol (96 percent).

Propyl Hydroxybenzoate.

Butyl Hydroxybenzoate.

Potassium Dihydrogen Orthophosphate.

Disodium Hydrogen Orthophosphate Anhydrous.

Sodium Chloride.

Saccharin Sodium.

Sorbitol Solution BPC 1973 (Non-crystallising).

Mint Flavour IFF 17:42:3632.

Purified Water.

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.

Shelf life

2 years when stored below 25°C.

Special precautions for storage

ZANTAC Syrup should be stored below 25°C.

Nature and contents of container

ZANTAC Syrup: 300mL presentation in a glass bottle.

Instructions for use/handling

None.

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Medicines Classification

Prescription Only Medicine

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