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.

Effervescent Tablets:
Ranitidine 150 mg or 300 mg.

Injection:
Ranitidine 50 mg in 2 ml aqueous solution (25 mg/ml) or 5 ml aqueous solution (10 mg/ml).

PHARMACEUTICAL FORM
Oral Formulations
Syrup.
Tablets: film-coated and effervescent.
Parenteral Formulation
Injection.

CLINICAL PARTICULARS
Indications

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

Oral formulations:

- 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.

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.

- *Children/Infants (1 month to 11 years)*

Oral formulations:

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

Injection:

- Treatment of peptic ulcer
- Treatment of gastro-oesophageal reflux, including reflux oesophagitis and symptom relief of gastro-oesophageal reflux disease
- Prophylaxis of stress ulceration in seriously ill-patients.

Dosage and Administration

General Information:
ZANTAC effervescent tablets should be placed in half a glass of water (minimum 75 ml) and allowed to dissolve completely before swallowing, swirl the glass if necessary. For 300 mg doses a volume of 150 ml is recommended.
ZANTAC effervescent tablets contain aspartame.

Syrup:
ZANTAC syrup contains approximately 7.5%w/v ethanol (alcohol), i.e. up to 405 mg per 5ml 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.

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.

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/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.

Injection:
Limited data exist on the administration of i.v. ranitidine to children. *ZANTAC* Injection may be given as a slow (over 2 min) i.v. injection, up to a maximum of 50 mg every 6 to 8 hours. This recommendation is derived from adult clinical studies and pharmacokinetic data in paediatric patients.

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 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).
As *ZANTAC* effervescent tablets contain aspartame they should be used with caution in patients with phenylketonuria.
ZANTAC effervescent tablets contain sodium *(see List of Excipients for sodium content)*. Care should therefore be taken in treating patients in whom sodium restriction is indicated.
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_2- 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.

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 (≥ 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, 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 5ml spoonful (approximately a teaspoonful) which is equivalent to about 11ml of beer or 5ml 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.
Clinicians should be aware of the sodium content of *ZANTAC* effervescent tablets *(see List of Excipients).*

Pharmacodynamics

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 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 ^{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 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.

Injection:

- **Neonates (under 1 month)**

Limited pharmacokinetic data suggests that plasma clearance of ranitidine may be reduced and half-life increased in neonates.

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

Syrup:
Hydroxypropyl methylcellulose 2906 or 2910 (4000 cP)
Ethanol (96 percent)
Propyl hydroxybenzoate
Butyl hydroxybenzoate
Potassium dihydrogen orthophosphate
Disodium hydrogen orthophosphate anhydrous
Sodium chloride
Saccharin sodium
Sorbitol 70 per cent (Non–crystallising)
Mint flavour IFF 17:42:3632
Purified water

Tablets:
Tablet core:
Microcrystalline cellulose
Croscarmellose sodium (300 mg tablet only)
Magnesium stearate
Film coat:
Opadry white OY–S–7232
Purified water

Effervescent Tablets:
Monosodium citrate anhydrous
Sodium hydrogen carbonate
Aspartame
Povidone K30
Sodium benzoate
Orange flavour IFF 6
Grapefruit flavour IFF 18 C222
Dehydrated alcohol or technical use alcohol
Ranitidine 150 mg and 300 mg effervescent tablets contain 14.2 mEq (327 mg) and 20.7 mEq (476 mg) of sodium, respectively.

Injection:
25 mg/ml:
Disodium hydrogen orthophosphate
Sodium Chloride
Potassium dihydrogen orthophosphate anhydrous
Water for injections
Nitrogen.

10 mg/ml:
Water for injections.

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.*

Shelf–Life
The expiry date is indicated on the packaging.

Special Precautions for Storage
ZANTAC syrup should be stored below 25°C.
ZANTAC film-coated tablets and effervescent tablets should be stored at a temperature below 30°C.

Injection:
Protect from light.
ZANTAC injection should not be autoclaved.
25 mg/ml: Store below 25°C.
10 mg/ml: Store below 25°C.

Nature and Contents of Container

Syrup:
Amber glass bottle (hydrolytic class III) with child resistant cap.

Tablets:
The tablets are packed either in foil strips or double foil blisters.

Effervescent Tablets:
The tablets are packed either in foil strips or double foil blisters.

Injection:
Clear type 1 glass ampoules.

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.

Manufactured by:
GlaxoSmithKline Manufacturing S.p.A, Parma, Italy

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