ZANTAC® TABLETS, DISPERSIBLE TABLETS, EFFERVESCENT TABLETS, SYRUP AND INJECTION

PRODUCT INFORMATION

NAME OF THE MEDICINE: Ranitidine hydrochloride

Structure:

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\text{CH}_3\text{N} \quad \text{O} \quad \text{CH}_3 \\
\text{S} \quad \text{N} \quad \text{H} \\
\text{N} \quad \text{CHNO}_2 \\
\text{CH}_3
\]

HCl

CAS number: 66357-59-3
Molecular formula: C\textsubscript{13}H\textsubscript{22}N\textsubscript{4}O\textsubscript{3}S.HCl
Molecular weight: 350.9
Chemical name: N-(2-(((5-((Dimethylamino)methyl)-2-furan-yl)methyl)thio)ethyl)N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride.

DESCRIPTION:

Ranitidine hydrochloride is a histamine H\textsubscript{2} - receptor antagonist. It is an aminoalkyl-substituted furan and is structurally different from cimetidine lacking the imidazole ring and the cyanoguanidine group. Ranitidine hydrochloride is a white to pale yellow granular solid with a melting point of about 140°C. It is freely soluble in water, with a partition co-efficient between n-octanol and water log P = 0.20. It has a slightly bitter taste and sulfurlike odour.

Zantac Tablets, Dispersible Tablets, Effervescent Tablets, Syrup and Injection contain the active ingredient ranitidine hydrochloride.

Zantac 150 mg Tablets contain the following excipients: magnesium stearate, microcrystalline cellulose, hypromellose, titanium dioxide and glycerol triacetate.

Zantac 300 mg Tablets contain the following excipients: croscarmellose sodium, magnesium stearate, microcrystalline cellulose, hypromellose, titanium dioxide and glycerol triacetate.

Zantac 150 mg Dispersible Tablets contain the following excipients: croscarmellose sodium, hydroxypropyl cellulose, hypromellose, magnesium stearate, microcrystalline cellulose, Peppermint flavour 17.02.0608, saccharin sodium, titanium dioxide.

Zantac 150 mg Effervescent Tablets contain the following excipients: aspartame, Grapefruit Flavour No. 18C222 (17.01.9455), monosodium dihydrogen citrate, Orange Flavour No.6 (15.02.1003), povidone, sodium benzoate and sodium bicarbonate.

Zantac 300 mg Effervescent Tablets contain the following excipients: aspartame, Grapefruit Grapefruit Flavour No. 18C222 (17.01.9455), monosodium dihydrogen citrate, Orange Flavour No.6 (15.02.1003), povidone, sodium benzoate and sodium bicarbonate.

Zantac Syrup contains the following excipients: butyl hydroxybenzoate, ethanol, hypromellose, Mint flavour 17.42.3632, monobasic potassium phosphate, propyl hydroxybenzoate, saccharin sodium, sodium chloride, dibasic sodium phosphate anhydrous, sorbitol solution, water (purified).
Zantac Injection contains the following excipients: monobasic potassium phosphate, sodium chloride, dibasic sodium phosphate, water for injections.

PHARMACOLOGY:

Animal experiments both *in vitro* and *in vivo* have established that ranitidine is a selective, competitive antagonist of histamine at \( H_2 \) - receptor sites. Ranitidine has no significant interaction at histamine \( H_1 \) - receptors, muscarinic receptors or beta-adrenoceptors. Ranitidine is a potent inhibitor of gastric secretion in the rat and dog.

All the evidence from human studies is compatible with a selective, competitive antagonism of histamine \( H_2 \) - receptors by ranitidine in man. Oral or intravenous administration of ranitidine inhibits both basal gastric secretions and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. On a weight basis ranitidine is between 4 and 9 times more potent than cimetidine.

After oral administration of ranitidine, the plasma concentrations of ranitidine achieved are directly related to the dose administered. A plasma ranitidine concentration of 50-100 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%.

Inhibition of pentagastrin-induced gastric acid secretion increases with dose, being approximately 90% two hours after an oral 150 mg dose and a significant effect is still evident 12 hours after this dose. In 10 patients with duodenal ulcer, 150 mg ranitidine given orally every 12 hours significantly reduced mean 24 hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90% whereas cimetidine (200 mg three times daily and 400 mg at night) reduced mean 24 hour hydrogen ion activity by 48% and nocturnal gastric acid output by 70%.

Pepsin secretion is also inhibited by ranitidine, but secretion of gastric mucus is not affected. Ranitidine does not alter the secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancreozymin. Reduction in gastric acid secretion induced by ranitidine 150 mg twice daily for 7 days did not cause bacterial overgrowth in the stomach.

Pulse rate, blood pressure, electrocardiogram and electroencephalogram were not significantly affected in man following recommended doses of ranitidine.

Chronic ranitidine therapy (300 mg/day for 28 days) had no effect on serum prolactin, gastrin, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone, gonadotrophins, testosterone, oestriol, progesterone or cortisol levels.

One study in 30 male duodenal ulcer patients showed a significant decrease in basal thyroxine levels after 4 weeks' treatment with 300 mg ranitidine daily, but no significant change in thyroid stimulating hormone was noted. Acute administration of 50 mg ranitidine intravenously had no effect on plasma aldosterone in healthy male volunteers whereas it caused a significant reduction in vasopressin. Cimetidine 200 mg intravenously had a similar effect on vasopressin.

Pharmacokinetics:

**Absorption**

Peak plasma levels occur about 2-3 hours after oral administration of ranitidine. Absorption is not significantly altered by food or concurrent antacid administration.

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 580 ng/mL) occurred after 1 to 3 hours. Two distinct peaks or a plateau in the absorption phase suggest reabsorption of drug secreted into the intestine. The absolute bioavailability of ranitidine is
50 to 60%, and plasma concentrations increase proportionally with increasing dose up to 200 mg. Bioavailability of ranitidine is approximately 50%. Serum protein binding of ranitidine in man is in the range 10-19%. The elimination half-life is approximately 2 hours.

**Distribution**
Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

**Metabolism**
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 and small amounts of desmethylranitidine and the furoic acid analogue. The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% after oral administration of the drug.

**Excretion**
Plasma concentrations decline bi-exponentially, with a terminal half-life of 2 to 3 hours. The major route of elimination of unchanged asenapine is renal. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

**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 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.

Impairment of renal function requires a reduction in dosage (see PRECAUTIONS). Impairment of liver function may increase the bioavailability of ranitidine but has no significant effect on the elimination half-life. However, in the presence of normal renal function, no dosage reduction for oral or intravenous ranitidine appears necessary in patients with hepatic impairment.

**INDICATIONS:**
1. Short-term treatment of proven duodenal ulcer and gastric ulcer, including intravenous use for prophylaxis against recurrent haemorrhage.
2. Maintenance treatment to reduce the risk of relapse in duodenal ulcer.
3. Maintenance treatment for periods up to one year to reduce the risk of relapse in patients with documented healing of benign gastric ulcer.
4. Treatment of gastrinoma (Zollinger-Ellison syndrome).
5. Short-term symptomatic treatment of reflux oesophagitis unresponsive to conservative anti-reflux measures and simple drug therapies such as antacids.
6. Maintenance treatment to reduce the risk of relapse of reflux oesophagitis.
7. Treatment of scleroderma oesophagitis.

The intravenous injection is indicated where oral treatment is inappropriate.

**CONTRAINDICATIONS:**
Patients with known hypersensitivity to any component of the preparation.

**PRECAUTIONS:**

**Gastric ulcer:** Treatment with a histamine H₂ - antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where
gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with Zantac Syrup, Tablets or Injection is instituted.

**Effects on fertility:** There are no data on the effects of ranitidine on human fertility. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine.

**Use in pregnancy:** Pregnancy category: B1. The safety of ranitidine in pregnancy has not been established. Ranitidine crosses the placenta. Zantac should only be used during pregnancy if considered essential. If the administration of Zantac is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the foetus.

**Use in lactation:** Ranitidine is secreted in breast milk in lactating mothers, but the clinical significance of this has not been fully evaluated. Zantac should only be used by nursing mothers if considered essential.

**Use in impaired renal function:** Ranitidine is excreted via the kidney and in the presence of renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly in the presence of significant renal impairment, serum levels should be monitored and dosage adjustments made. The clearance of ranitidine is increased during haemodialysis.

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

**Long-term use:** The risk of ulcer recurrence is determined by many factors. In some cases, long periods of treatment may be necessary and/or repeated. Evidence from controlled clinical trials of up to 18 months continuous treatment with Zantac has not revealed any undue untoward effects.

**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.

**Higher doses:** The use of higher than recommended doses of intravenous H₂ - antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

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

**Gastric pH:** Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated ICU patients receiving mechanical ventilation.

Zantac Effervescent Tablets contain sodium (see PRESENTATION AND STORAGE CONDITIONS). Care should therefore be taken in treating patients in whom sodium restriction is indicated. As Zantac Effervescent Tablets contain aspartame they should be used with caution in patients with phenylketonuria.

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).

**INTERACTIONS WITH OTHER MEDICINES:**
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).

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 two hours.

ADVERSE 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 clear in many cases. Headache, sometimes severe, has been reported in a very small proportion of patients.

**Central Nervous System:** Rarely, malaise, dizziness, somnolence, insomnia and vertigo. 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. There have been a few reports of reversible blurred vision suggestive of a change in accommodation. Reversible impotence has been reported rarely.

**Cardiovascular:** As with other H₂ - receptor antagonists rare reports of tachycardia, bradycardia, premature ventricular beats, AV block, and asystole.

**Gastrointestinal:** Constipation, diarrhoea, nausea/vomiting, abdominal discomfort/pain.

**Hepatic:** Transient and reversible changes in liver-function tests can occur. In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg intravenously four times daily for 7 days, and in 4 of 24 subjects receiving 50 mg intravenously four times daily for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

**Musculoskeletal:** Rare reports of arthralgias and myalgia.
**Haematologic:** Rare reports of agranulocytosis or pancytopenia, sometimes with marrow hypoplasia or aplasia have been reported. Blood count changes (leucopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible.

**Endocrine:** Controlled studies in animals and man have shown no stimulation of any pituitary hormone by ranitidine, no anti-androgenic activity, and cimetidine-induced gynaecomastia and impotence in hypersecretory patients have resolved when ranitidine was substituted. However, occasional cases of breast conditions such as gynaecomastia and galactorrhoea, impotence and loss of libido have been reported in male patients receiving ranitidine but the incidence did not differ from that in the general population.

**Integumental:** Rash including rare cases of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

**Renal:** Very rare cases of acute interstitial nephritis have been reported.

**Other:** Rare cases of hypersensitivity reactions (eg, fever, bronchospasm, anaphylactic shock, urticaria, angioneurotic oedema, hypotension, chest pain, rash, eosinophilia), small increases in serum creatinine. Acute pancreatitis has been reported rarely.

**DOSAGE AND ADMINISTRATION:**

Zantac may be administered by mouth, by intravenous injection or by slow intravenous infusion.

**Zantac Tablets, effervescent tablets and syrup:**

1. **Acute duodenal or gastric ulceration:**
   - 300 mg taken as a single dose at bedtime, or 150 mg taken twice daily, in the morning and at bedtime.
   
   It is not necessary to time the dose in relation to meals. In most cases healing will occur in four weeks although a small number of patients may require an additional 2-4 weeks' therapy.

2. **Maintenance treatment:**
   - 2.1 Duodenal ulcer: 150 mg taken at night. As smoking is associated with a higher rate of ulcer relapse, patients should be advised to stop smoking. In patients unable to stop smoking, a dose of 300 mg at night provides additional therapeutic benefit.
   - 2.2 Gastric ulcer: 150 mg taken at night for a period of one year.

3. **Gastrinoma (Zollinger-Ellison syndrome):**
   - 150 mg taken 3 times daily initially and increased, as necessary, to 600-900 mg/day.

4. **Prophylaxis against recurrent haemorrhage in patients bleeding from peptic ulceration:** This should be by intravenous injection or infusion.

5. **Oesophagitis:**
   - 300 mg taken as a single dose at bedtime or 150 mg taken twice daily in the morning and at bedtime. It is not necessary to time the dose in relation to meals.
   
   In severe reflux oesophagitis the efficacy of 300 mg, taken as a single dose at bedtime, has been established for up to 3 months.

6. **Maintenance Treatment:**
   - 6.1 Reflux oesophagitis: 150 mg taken twice daily in the morning and at bedtime.
Zantac Effervescent Tablets:
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. The effervescent formulations contain aspartame.

Zantac Syrup:
Zantac Syrup contains approximately 7.5%w/v ethanol (alcohol), i.e. up to 375 mg per 5 mL spoonful (approximately a teaspoonful).

Zantac Injection:
Zantac Injection may be given either as a slow intravenous injection of 50 mg (e.g., 2 mL diluted in 20 mL 0.9% sodium chloride and given as a slow injection over not less than 5 minutes), which may be repeated every six to eight hours; or as an intravenous infusion at a rate of 25 mg per hour for two hours; the infusion may be repeated at six to eight hour intervals.

Zantac Injection is a clear, colourless to pale yellow liquid.

Stability in intravenous infusion fluids:
Zantac Injection has been shown to be compatible with the following intravenous infusion fluids: 0.9% Sodium Chloride BP, 5% Glucose BP, 0.18% Sodium Chloride and 4% Glucose BP, 4.2% Sodium Bicarbonate BP and Hartmann’s Solution. However, Zantac Injection does not contain any anti-microbial preservative. To reduce microbial contamination hazards, the admixture should be used as soon as practicable after preparation. All unused admixtures of Zantac Injection with infusion fluids should be discarded 24 hours after preparation. Zantac Injection should not be autoclaved.

OVERDOSAGE:
There has been virtually no experience with overdosage with Zantac Injection and limited experience with oral doses of ranitidine. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience. (see ADVERSE EFFECTS). In the case of the Effervescent Tablets, clinicians should be aware of the sodium content (see PRESENTATION AND STORAGE CONDITIONS). Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

Zantac Syrup contains approximately 7.5%w/v ethanol (alcohol), i.e. up to 375 mg per 5 mL spoonful (approximately a teaspoonful). 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.

Rapid bolus injection of 300 mg intravenously (six times the recommended dose which should be given slowly) caused dizziness and peripheral vasodilatation.

Contact the Poisons Information Centre (telephone 131126) for advice on overdose management.

PHARMACEUTICAL PRECAUTIONS:
Dilution of Zantac Syrup with Syrup BP or Sorbitol solution is not recommended as this may result in precipitation.

PRESENTATION AND STORAGE CONDITIONS:
Zantac 150 mg Tablets are available as white film-coated tablets engraved “GX EC2” on one face and plain on the other. The tablets contain 150 mg ranitidine (as hydrochloride) and are available in packs of 6, 60 and 90 tablets in foil blister packs.

Zantac 300 mg Tablets are available as white capsule-shaped, film-coated tablets engraved “GX EC3” on one face and plain on the other. The tablets contain 300 mg ranitidine (as hydrochloride) and are available in packs of 4 and 30 tablets in foil blister packs.

Zantac 150 mg Dispersible Tablets are available as white, capsule-shaped, film-coated tablets with a breakline on one face. The tablets contain 150 mg ranitidine (as hydrochloride) and are available in packs of 10 and 60 tablets in foil strips.

Zantac 150 mg Effervescent Tablets are available as white to pale yellow, round, bevelled tablets debossed “GS LHK” on one side and flat on the other. The tablets contain 150 mg of ranitidine (as hydrochloride) and are available in packs of 10, 30 or 60 tablets in polypropylene tubes or in strip packs of 4 tablets. Each 150 mg tablet contains 328 mg (14.3 mEq) sodium.

Zantac 300 mg Effervescent Tablets are available as white to pale yellow, round, flat, bevelled tablets debossed “GS MJG” on one side and flat on the other. The tablets contain 300 mg of ranitidine (as hydrochloride) and are available in packs of 15 or 30 tablets in polypropylene tubes or in strip packs of 4 tablets. Each 300 mg tablet contains 479 mg (20.8 mEq) sodium.

Zantac Syrup contains 150 mg ranitidine (as hydrochloride) in each 10 mL of a peppermint flavoured sugar-free oral solution and is available in 300 mL amber glass bottles.

Zantac Injection is available as 50 mg ranitidine (as hydrochloride) in 2 mL ampoules in boxes of 5. The Injection is buffered with potassium acid phosphate 0.096% w/v and anhydrous sodium phosphate 0.240% w/v to pH 7.

Not all strengths, dose forms, pack sizes and container types are being distributed in Australia.

**Storage Conditions:**

Zantac 150 mg Tablets and Zantac 300 mg Tablets should be stored below 30°C, in a dry place.

Zantac 150 mg Dispersible Tablets should be stored below 30°C, in a dry place.

Zantac 150 mg Effervescent Tablets and Zantac 300 mg Effervescent Tablets should be stored below 25°C. Protect from moisture.

Zantac Syrup 150 mg/10 mL should be stored below 25°C

Zantac Injection 50 mg/2 mL should be stored below 25°C.

**NAME AND ADDRESS OF THE SPONSOR:**

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067

**POISON SCHEDULE OF THE MEDICINE:** S4

**DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG):** 13 August 1991