Product Monograph

PrZANTAC®

ranitidine tablets USP
ranitidine injection USP
ranitidine oral solution USP

Histamine H_2-receptor antagonist

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ACTIONS AND CLINICAL PHARMACOLOGY

Ranitidine is an antagonist of histamine at gastric H_2-receptor sites. Thus, ranitidine inhibits both basal gastric secretion 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. Inhibition of gastric acid secretion has been observed following intravenous, intraduodenal and oral administration of ranitidine. This response is dose-related, a maximum response being achieved at an oral dose of 300 mg/day.

Pepsin secretion is also inhibited 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.

Ranitidine is rapidly absorbed after oral administration of 150 mg ranitidine, peak 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. These plasma concentrations are not significantly influenced by the presence of food in the stomach at the time of the oral administration nor by regular doses of antacids.

Bioavailability of oral ranitidine is approximately 50% to 60%. Serum protein binding of ranitidine in man is in the range of 10 to 19%. The elimination half-life is approximately 2 to 3 hours. The principal route of excretion is the urine (40% recovery of free and metabolized drug in 24 hours).

There is a significant linear correlation between the dose administered and the inhibitory effect upon gastric acid secretion for oral doses up to 300 mg. A plasma ranitidine concentration of 50 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%. Estimates of the IC_{50} range from 36 to 94 ng/mL. Following the administration of 150 mg ranitidine orally, plasma concentrations in excess of this lasted for more than 8 hours and after 12 hours, the plasma concentrations were sufficiently high to have a significant inhibitory effect upon gastric secretion. In patients with duodenal ulcer, 150 mg oral ranitidine every 12 hours significantly reduced mean 24-hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90%. Furthermore, 300 mg oral ranitidine at night is as effective in reducing 24-hour intragastric acidity as 150 mg ranitidine given orally twice daily.

Following administration of 50 mg ranitidine injection intramuscularly, plasma concentrations in excess of 100 ng/mL were achieved within 5 minutes and remained above this level for 4 to 6 hours.

Intravenous infusion (rate: 0.125 mg/kg/hour) produced a rise of intragastric pH between 5.6 and 7.0 after 2 hours and maintained this level over the 24 hour period when administered to seriously ill patients. The volume of gastric secretion was reduced by more than 55%. Doubling the infusion rate to 0.25 mg/kg/hour produced no further increase in gastric acid inhibition.

A single 50 mg intravenous bolus dose of ranitidine injection produced significant acid inhibition 8 to 9 hours after administration. When 13 seriously ill patients with 2 or more risk factors (shock, sepsis, respiratory failure, jaundice, renal insufficiency or peritonitis) were treated with a 50 mg intravenous bolus dose of ranitidine injection followed by a continuous infusion of 0.2 mg/kg/hour, the number of 'at risk' days (gastric pH less than 3.5 at 3 consecutive four-hour aliquots) was approximately half that of placebo treated patients.

Tablets

In respect of both 24-hour acidity and nocturnal acid output, an oral dose of ranitidine 150 mg twice daily was superior to cimetidine 200 mg three times daily and 400 mg at night ($p<0.001$ and $p<0.05$, respectively).

Treatment of volunteers with an oral dose of ranitidine 150 mg twice daily for 7 days did not cause bacterial overgrowth in the stomach.

Volunteers treated with an oral dose of ranitidine have reported no significant gastrointestinal or central nervous system side effects; moreover pulse rate, blood pressure, electrocardiogram and electroencephalogram were not significantly affected in man following ranitidine administration.

In healthy human volunteers and patients, ranitidine, when administered orally did not influence plasma levels of the following hormones: cortisol, testosterone, estrogens, growth hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, aldosterone or gastrin; although like cimetidine, ranitidine reduced vasopressin output. Treatment for up to 6 weeks with ranitidine 150 mg twice daily by mouth did not affect the human hypothalamic-pituitary-testicular-ovarian or -adrenal axes.

Injection

Intramuscular ranitidine is fully bioavailable in comparison to intravenous ranitidine. The median elimination half-life of ranitidine injection 50 mg, administered intravenously or intramuscularly was found to be 2.3 hours (range 120 to 160 minutes). In comparison, the elimination half-life following oral administration is approximately 2 to 3 hours. However, the half-life of ranitidine in patients with renal dysfunction is prolonged. In a study of 27 patients with renal dysfunction (plasma creatinine concentration greater than 300 µmol/litre) therapeutic plasma levels of ranitidine were shown to be achieved without risk of drug accumulation, if half the normal dose of ranitidine was administered.

Ranitidine injection is well tolerated following intravenous administration at dose levels of up to 100 mg 4 times daily. It is evident that these levels are in excess of those recommended for normal clinical use.

At 50 mg intravenously, ranitidine injection had no effect on prolactin levels. Only at the 300 mg IV dose level was there an increase in prolactin secretion, which was equivalent to that produced by 200 mg of cimetidine administered intravenously.

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.

INDICATIONS AND CLINICAL USE

ZANTAC® (ranitidine hydrochloride) Tablets, Injection, and Oral Solution are indicated for the treatment of duodenal ulcer, benign gastric ulcer, reflux esophagitis, post-operative peptic ulcer, Zollinger-Ellison Syndrome, and other conditions where reduction of gastric secretion and acid output is desirable. These include the following:

- the treatment of nonsteroidal anti-inflammatory drug (NSAID)- induced lesions, both ulcers and erosions, and their gastrointestinal (GI) symptoms and the prevention of their recurrence;
- the prophylaxis of GI hemorrhage from stress ulceration in seriously ill patients;
- the prophylaxis of recurrent hemorrhage from bleeding ulcers;
- the prevention of Acid Aspiration Syndrome from general anaesthesia in patients considered to be at risk for this, including obstetrical patients in labour, and obese patients.

In addition, ZANTAC® is indicated for the prophylaxis and maintenance treatment of duodenal or benign gastric ulcer in patients with a history of recurrent ulceration.

CONTRAINDICATIONS

ZANTAC® (ranitidine hydrochloride) is contraindicated for patients known to have hypersensitivity to ranitidine or to any ingredient in the formulation. For a complete listing, see COMPOSITION.

WARNINGS

Gastric Ulcer

Treatment with a histamine H_2-antagonist may mask symptoms associated with carcinoma of the stomach and, therefore, may delay diagnosis of that condition. Accordingly, where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with ZANTAC® (ranitidine hydrochloride) is instituted.

Concomitant NSAID Use

Regular supervision of patients who are taking non-steroidal anti-inflammatory drugs concomitantly with ZANTAC® is recommended especially in the elderly and in those with a history of peptic ulcer. Baseline endoscopy and histological evaluation is necessary to rule out gastric carcinoma.

Use in Patients with a History of Acute Porphyria

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

Use in Pregnancy and Nursing Mothers

The safety of ZANTAC® in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of ZANTAC® induced impaired fertility or harm to the fetus. Ranitidine crosses the placenta. Nevertheless, 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 fetus.

ZANTAC® is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated. Like other drugs, ZANTAC® should only be used during nursing if considered essential.

Children

Experience with ZANTAC® products in children is limited. It has, however, been used successfully in children aged 8 to 18 years in oral doses up to 150 mg twice daily.

PRECAUTIONS

General

Injection

Bradycardia in association with rapid administration of ZANTAC® (ranitidine hydrochloride) Injection has been reported rarely, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded. (See ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION).

The use of higher than recommended doses of IV H_2-antagonists has been associated with rises in liver enzymes when treatment has been extended beyond five days.

Use in Impaired Renal Function

ZANTAC® is excreted via the kidneys and, in the presence of renal impairment, plasma levels of ZANTAC® are increased and elimination prolonged. Accordingly, it is recommended in such patients, to decrease the dosage of ZANTAC® by one half. Accumulation of ZANTAC® with resulting elevated plasma concentrations will occur in patients with renal impairment (creatinine clearance less than 50 ml/min); a recommended daily dose of oral ranitidine in such patients should be 150 mg.

Interaction with Other Drugs

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) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitnib).

Sporadic cases of drug interactions have been reported in elderly patients involving both hypoglycaemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials with theophylline and ZANTAC® have not shown interaction.

If high doses (two grams) of sucralfate are coadministered with ZANTAC®, the absorption of ZANTAC® may be reduced. This effect is not seen if sucralfate is taken at least two hours after ZANTAC® administration.

Special Populations

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).

Use in the Elderly

Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with ZANTAC® is instituted. Elderly patients receiving non-steroidal anti-inflammatory drugs concomitantly with ZANTAC® should be closely supervised.

As with all medication in the elderly, when prescribing ZANTAC®, consideration should be given to the patient's concurrent drug therapy. Sporadic cases of drug interaction have been reported in elderly patients involving both hypoglycaemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials with theophylline and ZANTAC® have not shown interaction. Elderly patients may be at increased risk for confusional states and depression.

ADVERSE REACTIONS

Tablets, Injection, and Oral Solution

The following adverse reactions have been reported as events in clinical trials or in the routine management of patients treated with ZANTAC® (ranitidine hydrochloride). A cause and effect relationship to ZANTAC® is not always established.

Central Nervous System

Headache, sometimes severe; malaise; dizziness; somnolence; insomnia; vertigo; and reversible blurred vision suggestive of a change in accommodation. Isolated cases of reversible mental confusion, agitation, depression, hallucinations have been reported, predominantly in severely ill elderly patients. In addition, reversible involuntary movement disorders have been reported rarely.

Cardiovascular

Isolated reports of tachycardia, bradycardia, premature ventricular beats, AV block have been noted. Asystole has been reported in very few individuals with and without predisposing conditions following IV administration and has not been reported following oral administration of ZANTAC® (See PRECAUTIONS, DOSAGE AND ADMINISTRATION).

Gastrointestinal

Constipation, diarrhea, nausea/vomiting and abdominal discomfort/pain.

Hepatic

In normal volunteers, transient and reversible SGPT and SGOT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving ranitidine 100 mg qid intravenously for seven days, and in 4 of 24 subjects receiving 50 mg qid intravenously for five days. Therefore, it may be prudent to monitor SGOT and SGPT in patients receiving intravenous treatment for five days or longer and in those with pre-existing liver diseases. With oral administration, there have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. In such circumstances, ranitidine should be discontinued immediately. These are usually reversible, but in exceedingly rare circumstances, death has occurred.

Renal

Very rare cases of acute interstitial nephritis have been reported.

Musculoskeletal

Rare reports of arthralgia and myalgia.

Haematologic

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

Endocrine

No clinically significant interference with endocrine or gonadal function has been reported. There have been a few reports of breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea).

Dermatologic

Rash, including cases suggestive of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

Other

Rare cases of hypersensitivity reactions (including chest pain, bronchospasm, fever, rash, eosinophilia, anaphylaxis, urticaria, angioneurotic edema, hypotension) and small increases in serum creatinine have occasionally occurred after a single dose. Acute pancreatitis and reversible impotence has been reported rarely.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed drug from the gastrointestinal tract (including activated charcoal or syrup of ipecac), clinical monitoring and supportive therapy should be employed.

For management of a suspected drug overdose, contact your regional Poison Control Centre.

DOSAGE AND ADMINISTRATION

Tablet, and Oral Solution Administration

Duodenal ulcer or benign gastric ulcer

300 mg once daily at bedtime or 150 mg twice daily taken in the morning and before retiring. It is not necessary to time the dose in relation to meals. In most cases of duodenal ulcer and benign gastric ulcer, healing will occur in four weeks. In the small number of patients whose ulcers may not have fully healed, these are likely to respond to a further four week course of therapy. In the treatment of duodenal ulcers, 300 mg twice daily for 4 weeks may be of benefit when more rapid healing is desired.

Maintenance therapy

Duodenal ulcers, benign gastric ulcers: Patients who have responded to short-term therapy, particularly those with a history of recurrent ulcer, may benefit from chronic maintenance therapy at a reduced oral dosage of 150 mg once daily at bedtime.

In the management of duodenal ulcers, smoking is associated with a higher rate of ulcer relapse (up to 9.2 times higher in one trial), and such patients should be advised to stop smoking. In those patients who fail to comply with such advice, 300 mg nightly provides additional therapeutic benefit over the 150 mg once daily dosage regimen.

Reflux esophagitis

Acute treatment

300 mg once daily at bedtime, or alternatively 150 mg twice daily, taken in the morning and before retiring for up to eight weeks. In patients with moderate to severe esophagitis, the dosage of ranitidine may be increased to 150 mg four times daily for up to 12 weeks.

Long-term Management

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

Post-operative peptic ulcer

150 mg twice daily, taken in the morning and before retiring.

Pathological hypersecretory conditions (Zollinger-Ellison Syndrome)

150 mg three times daily may be administered initially. In some patients, it may be necessary to administer ZANTAC® 150 mg doses more frequently. Doses should be adjusted to individual patient needs. Doses up to six grams per day have been well tolerated.

Treatment of NSAID-induced lesions (both ulcers and erosions) and their gastrointestinal symptoms and prevention of their recurrence

In ulcers following non-steroidal anti-inflammatory drug therapy or associated with continued non-steroidal anti-inflammatory drugs, 150 mg twice daily for 8-12 weeks may be necessary. For the prevention of non-steroidal anti-inflammatory drug associated ulcer recurrence, 150 mg twice daily may be given concomitantly with non-steroidal anti-inflammatory drug therapy.

Prophylaxis of acid aspiration syndrome (AAS)

150 mg the evening prior to anaesthesia induction is recommended, however, 150 mg two hours before anaesthesia induction is also effective. Alternatively, ZANTAC® Injection may be used. For the prevention of AAS in pre-partum patients who elect for anaesthesia, 150 mg every six hours may be employed, but if general anaesthesia is warranted, a non-particulate oral antacid (for example, sodium citrate) could supplement ZANTAC® therapy. In

an emergency situation, the use of alkalis, antacids, and meticulous anaesthetic technique is still necessary as ZANTAC® does not affect the pH and volume of the existing gastric content.

Prophylaxis of hemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent hemorrhage in patients bleeding from peptic ulceration who are currently managed by intravenous ZANTAC®

An oral dose of 150 mg twice daily may be substituted for the injection once oral feeding commences.

If necessary, ZANTAC® Oral Solution may be administered by orogastric or nasogastric tube as an alternative.

Note

A 150 mg dose of ranitidine is equivalent to 10 mL (2 teaspoonfuls) of ZANTAC® Oral Solution, and 300 mg ranitidine is equivalent to 20 mL (4 teaspoonfuls) of ZANTAC® Oral Solution.

Dosage for the Elderly

For all conditions listed above, the drug dosage for the elderly who are seriously ill should start at the lowest recommended dose and be adjusted as necessary with close supervision.

Patients over 50 years of age (see ACTIONS AND CLINICAL PHARMACOLOGY, Patients over 50 years of age).

Parenteral Administration

In some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or in patients unable to take oral medication, ZANTAC® may be administered parenterally according to the following recommendations:

Intramuscular Injection

50 mg (2 mL) every six to eight hours (no dilution is required).

Intravenous Injection

50 mg (2 mL) every six to eight hours. Dilute ZANTAC® Injection, 50 mg in compatible IV solution (see PHARMACEUTICAL INFORMATION, Dilution of Parenteral Products) to a total volume of 20 mL and inject over a period of <u>not less than five minutes</u> (See PRECAUTIONS). Parenteral administration may continue until oral feeding is commenced and, if there is still a risk, oral ZANTAC® may then commence.

Intermittent Intravenous Infusion

50 mg (2 mL) every six to eight hours. Dilute ZANTAC® Injection 50 mg in 100 mL of compatible IV solution (see PHARMACEUTICAL INFORMATION, Dilution of Parenteral Products) and infuse over 15 to 20 minutes. In some patients, it may be necessary to increase dosage. When this is required, the increases should be made by more frequent administration of a 50 mg dose, but generally should not exceed 400 mg per day.

In the prophylaxis of upper gastrointestinal hemorrhage from stress ulceration in seriously ill patients, a primary dose of 50 mg as a slow (over a period of not less than five minutes) intravenous injection followed by a continuous intravenous infusion of 0.125 - 0.250 mg/kg/hr may be preferred (See PRECAUTIONS). The higher infusion concentration (0.25 mg/kg/hr) should be reserved for patients who are unresponsive to a lower concentration (0.125 mg/kg/hr).

In the prophylaxis of hemorrhage from stress ulceration in seriously ill patients or prophylaxis of recurrent hemorrhage in patients bleeding from peptic ulceration, parenteral administration may continue until oral feeding is commenced and if there is still a risk, oral ZANTAC® may then commence.

For patients considered at risk of developing acid aspiration syndrome (Mendelson's Syndrome), 50 mg by intramuscular or slow (over a period of not less than 5 minutes) intravenous injection 45 to 60 minutes before induction of general anaesthesia. In an emergency situation, the use of alkalis, antacids, and meticulous anaesthetic technique is still necessary as ZANTAC® does not affect the pH and volume of the existing gastric content.

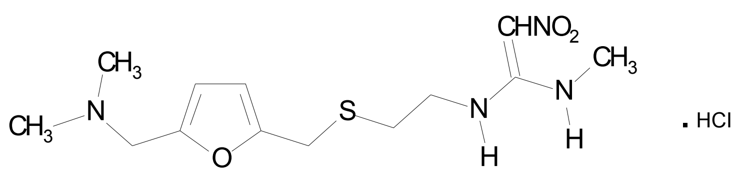
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: ranitidine hydrochloride

Chemical Name: N-{2-[({5-[(dimethylamino)-methyl]-2-furanyl} methyl)thio]ethyl}-N'-methyl-2-nitro-1, 1-ethenediamine, hydrochloride

Structural Formula:



Molecular Formula: $C_{13}H_{22}N_4O_3S \cdot HCl$

Molecular Weight: 350.87 (as hydrochloride salt)

Description: Ranitidine hydrochloride is a white to pale yellow granular substance. At room temperature, ranitidine hydrochloride is soluble in water, methanol, ethanol and chloroform (decreasing order). ZANTAC® Injection is a clear, colourless to light yellow liquid. The pH of the injection solution is 6.7 to 7.3.

COMPOSITION

ZANTAC® Tablets

150 mg	Each tablet contains 168 mg of ranitidine hydrochloride (150 mg ranitidine anhydrous free base). Tablets also contain the following excipients: microcrystalline cellulose and magnesium stearate. The film-coating suspension contains the following excipients: hydroxypropyl methylcellulose, triacetin, and titanium dioxide.
300 mg	Each tablet contains 336 mg of ranitidine hydrochloride (300 mg ranitidine anhydrous free base). Tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The film-coating suspension contains the following excipients: hydroxypropyl methylcellulose, triacetin, and titanium dioxide.

ZANTAC® Oral Solution

Contains 168 mg of ranitidine hydrochloride in 10 millilitres (150 mg ranitidine anhydrous free base/10 mL Oral Solution). Also contains the following excipients: hydroxypropyl methylcellulose, propylparaben, butylparaben, monobasic potassium phosphate, dibasic sodium phosphate, sodium chloride, sorbitol, sodium cyclamate, mint flavour, alcohol (7.5% w/v).

Each 5 mL (1 teaspoonful) therefore contains 75 mg ranitidine anhydrous free base.

ZANTAC® Injection

Each mL contains 28 mg ranitidine hydrochloride equivalent to 25 mg ranitidine anhydrous free base in Sterile Water for Injection for intravenous or intramuscular administration. Non-medicinal ingredients include phenol (5 mg/mL) as a preservative, disodium hydrogen orthophosphate (2.4 mg/mL), and potassium dihydrogen orthophosphate (0.96 mg/mL).

STORAGE AND STABILITY

ZANTAC® Tablets

Store between 2°C and 30°C. Protect from light.

ZANTAC® Oral Solution

Store at or below 25°C. Protect from light. Keep out of reach of children.

ZANTAC® Injection

Store between 2°C and 25°C. Protect from light.

ZANTAC® Injection should not be autoclaved.

Dilution of Parenteral Products

Intramuscular Injection

No dilution is required.

Intravenous Injection

ZANTAC® Injection for intravenous injection should be diluted to 20 mL (2.5 mg/mL) with one of the recommended diluents listed below.

Intermittent Intravenous Infusion

ZANTAC® Injection for intermittent intravenous infusion should be diluted to 100 mL (0.5 mg/mL) with one of the recommended diluents listed below. ZANTAC® Injection is compatible in polyvinyl chloride infusion bags and in glass with the following intravenous fluids:

- 0.9% sodium chloride
- 5% dextrose
- 0.18% sodium chloride and 4% dextrose
- 4.2% sodium bicarbonate
- Hartmann's solution

Admixtures of ZANTAC® Injection with 0.18% sodium chloride and 4% dextrose or 4.2% sodium bicarbonate or Hartmann's solution should be discarded after 24 hours. Although intravenous admixtures of ZANTAC® Injection with 5% dextrose or 0.9% sodium chloride may often be physically and chemically stable for longer periods, due to microbiological considerations, they are usually recommended for use within the maximum of 72 hours when refrigerated (2° to 8°C) followed by 24 hours at room temperature.

Hospitals and institutions that have recognized admixture programs and use validated aseptic techniques for preparation of intravenous solutions, may extend the storage time for ZANTAC® Injection in admixture with 5% Dextrose Injection or 0.9% Sodium Chloride Injection in polyvinyl chloride infusion bags, in concentrations of up to 2 mg/mL, to 35 days when stored under refrigeration at 2° to 8°C.

Note: As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitate, or discolouration or leakage should not be used.

Pharmaceutical Precautions

ZANTAC® Injection

ZANTAC® Injection should not be autoclaved.

AVAILABILITY OF DOSAGE FORMS

ZANTAC® Tablets

150 mg	White, round, biconvex, film-coated tablets engraved ZANTAC 150 on one face and GLAXO on the other, available in foil packs of 60 tablets and bottles of 100 and 500 tablets.
300 mg	White, capsule-shaped film-coated tablets engraved ZANTAC 300 on one face and GLAXO on the other, available in foil packs of 30 tablets and bottles of 60 tablets.

ZANTAC® Oral Solution

Clear, peppermint-flavoured oral solution, available in 300 mL bottles.

ZANTAC® Injection

ZANTAC® Injection is available in 2 mL unit dose colourless glass vials in packs of 10 and 40 mL multidose colourless glass vials in packs of 1.

PHARMACOLOGY

Animal Pharmacology

Ranitidine is a potent competitive reversible, selective antagonist of histamine at H_2-receptors *in vitro* and *in vivo*. Thus, ranitidine antagonised the actions of histamine at H_2-receptors in the rat isolated uterus and in the guinea pig isolated atrium. Ranitidine is not an anticholinergic agent. On a molar basis, ranitidine is 4 to 5 times more active than cimetidine with a pA_2 value of 7.2. In concentrations 1,000 times greater than those required to block H_2-receptors, it failed to block either H_1-receptors or muscarinic receptors in the guinea pig isolated ileum. The beta-adrenoceptor responses of the rat uterus and guinea pig atrium to isoprenaline were also unaffected by ranitidine.

Blockade of histamine H_2-receptors in the stomach *in vivo* is the pharmacological action of ranitidine with greatest immediate clinical relevance. Ranitidine inhibits gastric secretion induced by various secretagogues in both the rat and dog.

In the conscious dog with a Heidenhain pouch, ranitidine given orally or intravenously antagonised gastric acid secretion induced by histamine, pentagastrin and bethanechol. Ranitidine was 5 to 10 times more active than cimetidine. However, both ranitidine and cimetidine had similar time curves of action. Ranitidine also inhibited the gastric secretory response to food in the conscious fistulated dog.

Ranitidine inhibited acid secretion in the perfused stomach of the anaesthetised rat, and aspirin-induced gastric lesion formation in the conscious rat, both in the presence and absence of excess hydrochloric acid. Measurements of the ratio of mucosal blood flow to acid secretion show that the inhibitory action of ranitidine upon gastric acid secretion cannot be attributed to changes in blood flow.

There were no behavioural effects in the mouse and rat after oral administration of 800 mg/kg ranitidine. Cats and dogs dosed with ranitidine 80 mg/kg orally, exhibited no behavioural effects indicative of an action on the central nervous system, although at this high dose level in the dog there was an indication of peripheral vasodilation and skin irritation due to released histamine. Ranitidine, when coadministered with the following CNS modulating preparations; codeine, hexobarbitone, ethyl alcohol, chlordiazepoxide, chlorpromazine, imipramine, α-methyldopa, reserpine, apomorphine or pentylenetetrazol, did not alter the pharmacological effects of either preparation.

At a dose level 45 times the antisecretory ED_{50}, intravenous infusion of ranitidine had no effect on the heart rate, blood pressure or electrocardiogram of the anaesthetised dog. The respiratory system was unaffected by ranitidine after oral doses in the mouse, rat, rabbit, cat and dog and after intravenous doses in the dog.

In the conscious dog, ranitidine had no appreciable effect on blood pressure or heart rate when administered orally at 10 mg/kg. There were short-lived falls in diastolic blood pressure after an intravenous dose of 10 mg/kg, 370 times the antisecretory dose level. There was no evidence of arrhythmia nor of any electrocardiographic abnormality.

Long-term toxicity studies have shown that ranitidine does not possess antiandrogenic activity nor does it displace dihydrotestosterone from the androgen binding sites.

Metoclopramide, atropine and aspirin in the rat produced no change in the antisecretory activity of ranitidine.

The effect of ranitidine on anti-inflammatory drugs was varied. There was no effect on the anti-inflammatory action of prednisolone, but the anti-inflammatory action of indomethacin was enhanced. Administration of ranitidine reduced the frequency of aspirin- and indomethacin-induced gastric erosions. The antinociceptive action of aspirin was reduced after ranitidine treatment.

Ranitidine, unlike cimetidine, does not inhibit the hepatic mixed function oxygenase system. Spectral interaction studies have shown that whilst cimetidine binds strongly to cytochrome P_{450}, ranitidine has only weak affinity for this enzyme. Cimetidine is known to impair the metabolism of pentobarbitone and warfarin. In doses of up to 166 mg/kg in the rat, ranitidine had no effect on the pentobarbitone sleeping time or the pharmacokinetics and pharmacodynamics of warfarin.

Metabolism, Distribution and Excretion

The metabolism of ranitidine hydrochloride has been studied in four species of laboratory animal (mouse, rat, rabbit and dog) using radio-labelled drug. The drug was rapidly absorbed after oral administration. In the mouse, rat and rabbit between 30% and 60% of the administered radioactivity was excreted in the urine, the remainder being recovered in the feces.

In the mouse 47% was excreted in the urine within 24 hours. In the rat, N-demethylation of ranitidine was the major route of metabolism. 30% of the administered dose was excreted in the urine as unchanged drug, up to 14% as desmethylranitidine, 3-6% as the N-oxide and 4% as the S-oxide. In rat bile the major radioactive components were ranitidine and an unidentified metabolite known as "Fast-Running Metabolite" (FRM) which is thought to be a charge transfer complex of ranitidine with bile pigments.

In the rabbit, sulphoxidation of ranitidine was the major route of metabolism, 18% of the administered dose being excreted in the urine as unmetabolised ranitidine, 8% as S-oxide, 2-4% as the N-oxide, and 2-4% as desmethylranitidine.

In the dog up to 70% of the administered dose was excreted in the first 24 hours. About 40% of the drug was excreted in the urine as unchanged ranitidine and up to 30% as the N-oxide, N-oxidation being the main route of metabolism of ranitidine in the dog. The N-oxide was also the major radioactive component present in dog bile together with small amounts of unchanged ranitidine and FRM.

In the rat, rabbit and dog, less than 10.1% of ranitidine in plasma is protein bound. Within one to seven days of administration of radio-labelled drug in the rat and dog over 99% of the radioactivity was cleared from the body. In common with many drugs, radioactivity persisted in the uveal tract of these two species, the half-life in the dog uveal tract being of the order of 6 months. Ranitidine and its S-oxide have greater affinity for melanin than the desmethyl metabolite; the N-oxide is bound only to a small extent.

The placental transfer of radioactive ranitidine and its metabolites has been studied in the pregnant rat and rabbit. Whole body autoradiography of rat and rabbit fetuses showed that small amounts of radioactivity were present in the uveal tract of the fetal eye in both species, in the gall bladder and intestine of the rabbit fetus and in the bladder of the rat fetus. Radioactivity was also detected in the salivary and mammary glands of the maternal rat and at very low concentration, in the milk.

Human Pharmacokinetics

Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of ranitidine are in this range for up to 12 hours. There is a relationship between plasma concentrations of ranitidine and suppression of gastric acid production but wide interindividual variability exists.

Ranitidine is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring two to three hours after a 150 mg dose. The elimination half-life is 2 to 3 hours.

The major route of elimination is renal. After IV administration of 150 mg 3H-ranitidine, 98% of the dose was recovered, including 5% in feces 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 the feces 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.

Ranitidine is absorbed very rapidly after an intramuscular injection. Mean peak levels of 576 ng/mL occur within 15 minutes or less following a 50 mg intramuscular dose. Absorption from intramuscular sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous administration.

The principal route of excretion is the urine, with approximately 30% of the orally-administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is about 530 mL/min, indicating active tubular excretion, with a total clearance of 760 mL/min. The volume of distribution ranges from 96 to 142 L.

Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there are minor, but clinically insignificant alterations in ranitidine half-life, distribution, clearance and bioavailability.

Serum protein binding averages 15%.

The gastric antisecretory activity of ranitidine metabolites has been examined. In man, both the principal metabolite in the urine, the N-oxide (4% of the dose) and the S-oxide (1%) possess weak H_2-receptor blocking activity but desmethylranitidine (1%) is only 4 times less potent than ranitidine in the rat and half as potent as ranitidine in the dog.

CLINICAL TRIALS

In 6 clinical trials examining the healing of duodenal ulcers in 1,500 patients, a dose of 300 mg daily for 4 weeks was found to have an 83% healing rate; however, increasing the dose to 300 mg twice daily gave significantly better results (92% healed at 4 weeks; $p<0.001$).

BIOAVAILABILITY AND CLINICAL DATA

Bioavailability comparison between ZANTAC® Tablet and ZANTAC® Oral Solution (Study RAN-600).

A single dose, randomized, two-phase crossover bioavailability comparison between ZANTAC® Tablets and ZANTAC® Oral Solution was performed. Eighteen male volunteers with a median age of 25 years (range 22-32 years) shown to be free from renal impairment, hepatic disease or hypersensitivity to H_2 receptor antagonists participated in the study. Subjects were administered, after a 72 hour washout period, a single ranitidine dose consisting of either one 150 mg tablet or the equivalent dose of Oral Solution.

Aliquots of blood were drawn via an intravenous indwelling catheter at 0, 4, 8, 12, 16 and 20 hours post-dose. Plasma ranitidine concentrations were determined by RIA techniques.

The mean ± SEM serum ranitidine concentrations after either a 150 mg ZANTAC® dose administered as a tablet or Oral Solution is displayed below.

An overall summary of the pharmacokinetic parameters are shown below:

Pharmacokinetic Parameters for Eighteen Subjects Administered a Single Dose of either ZANTAC® Tablet or Oral Solution

	AUC (ng.hr/mL)	MRT (hr)	MAT (hr)	K_{el} (hr^{-1})	Half-Life (hr)	C_{max} (ng/mL)	T_{max} (hr)
Syrup Formulation	2577	5.17	1.44	0.273	2.55	493	3.3 (Median)
Tablet Formulation	2615	5.15	1.46	0.276	2.51	575	3.0 (Median)
Fail to Reject Hypothesis of No Difference	YES	YES	YES	YES	YES	NO**	YES**
Satisfy 75/75 Rule	YES	---	---	---	---	YES	NO*
Statistical Power to Detect a 20% Difference	95%	>99%	<0%	>99%	>99%	---	---

* 38.9% (7/18) of the subjects satisfied the 75/75 rule; 83% (15/18) of the subjects had a T_{max} for the syrup that was at least 75% of the T_{max} for the tablet.

** Wilcoxon Matched-Pairs Signed-Rank Test, $\alpha = 0.05$

No significant differences were observed in the area under the curve (AUC), mean residence time (MRT), mean absorption time (MAT), elimination rate constant (K_{el}) or terminal elimination half-life ($t_{½}$). Some variation was observed in maximum concentration (C_{max}) between the two formulations. The time of maximum concentration (T_{max}) does not demonstrate a significant variability in the rate of absorption between the two formulations. The investigators concluded that since the extent of absorption for ranitidine from the Oral Solution and tablet formulations were identical and the C_{max} of the Oral Solution were within 13% of those for the tablet formulation, the Oral Solution and tablet formulations are judged to be bioequivalent.

TOXICOLOGY

Toxicology, Impairment of Fertility, Carcinogenesis, and Mutagenesis

Ranitidine hydrochloride has been subjected to exhaustive toxicological testing which has demonstrated the lack of any specific target organ or any special risk associated with its clinical use.

Acute Toxicity Studies

In mice and rats, the intravenous LD_{50} is of the order of 75 mg/kg, whereas orally, even doses of 1,000 mg/kg are not lethal. In dogs, the oral minimum lethal dose is 450 mg/kg/day. High single doses of ranitidine (up to 80 mg/kg orally) show only minimal and reversible signs of toxicity, some of which are related to transitory histamine releases.

Long-Term Toxicity Studies

In the long-term toxicity and carcinogenicity studies, very high doses of ranitidine were given daily to mice (up to 2000 mg/kg/day) throughout their normal life-span, and to dogs (up to 450 mg/kg/day) for periods of up to one year.

These doses produced massive plasma ranitidine concentrations far in excess of those found in human patients receiving ranitidine at the recommended therapeutic dose. For example, in the dogs, peak plasma concentrations were in excess of 115 µg/mL and in mice basal plasma levels were in the range of 4-9 µg/mL. In man, after oral administration of 150 mg ranitidine, the mean peak plasma concentration (C_{max}) was between 360 and 650 ng/mL.

In the rat, doses as high as 2,000 mg/kg/day were well tolerated, the only morphological change seen was the increased incidence of accumulations of foamy alveolar macrophages in the lungs. The accumulations of these cells is a natural phenomena in aging rats and chronic administration of a wide variety of drugs has been known to contribute to this process. Therefore, it is unlikely that the pharmacologic concentrations of ranitidine administered to these rats contributed to this natural process.

In the six-week and six-month oral studies in the dog (100 mg/kg/day) loose feces were occasionally detected, while in the six-month study loose stools were accompanied on eight occasions by mucus-like material and sometimes by blood, mostly from one dog. Loose feces, salivation and vomiting were observed in the 54-week dog study.

In isolated cases, dogs passed red-stained feces which occasionally tested positive for occult blood. When the dose level was increased from 100 mg/kg/day to 225 – 450 mg/kg/day, no further red-stained feces were seen, suggesting that any relationship to ranitidine is unlikely. Post-mortem examination of the dogs revealed no ranitidine-induced changes in the alimentary tract.

One dog had marginally raised levels of plasma alanine aminotransferase and alkaline phosphatase during the six-week study. This same dog also showed some necrotic foci in the liver. Small lesions of focal necrosis and fibrosis were also seen in one piece of liver from one female dog treated with 100 mg/kg for six months. No other differences were detected by light and electron microscopic examination of the treated and control livers. Since the focal lesions were seen in only one dog and were restricted to one piece of liver, it suggests that they were not caused by ranitidine.

Muscular tremors, an inability to stand, and rapid respiration were seen on occasion in dogs treated with 225 mg/kg/day in the 54-week study. The prevalence of these observations was increased when the dose was increased to a toxic level of 450 mg/kg/day. One dog died: no specific pathological changes or reason for the death was discovered.

Changes in the colour or granularity of the tapetum lucidum of the eye were detected in three dogs receiving the highest dose of ranitidine (450 mg/kg/day) during the 54-week study. In one dog this change was considered to be related to treatment. The change, a pallor of the tapetum, was reversible. No changes were seen with light or electron microscopic examination of the eye. The changes in the tapetum are of no clinical significance in humans since (i) humans do not have a tapetum lucidum and (ii) the changes were only seen at toxic pharmacological concentrations of ranitidine.

The mean serum glutamic pyruvic transaminase values for dogs treated at 450 mg/kg/day were significantly greater, albeit marginally, than the control values. These enzyme increases were not accompanied by any histological changes.

Studies in which ranitidine was administered parenterally were performed. No sign of specific local irritation attributable to ranitidine was detected. In the rat, no biochemical or histopathological changes were observed at intravenous dose levels as high as 20 mg/kg. Specifically, no significant changes were found in the veins or subcutis. Mild lesions in some muscle samples were observed: usually, the cells were basophilic and smaller than normal; and the nuclei were swollen, more numerous, and sometimes had migrated to the centre of the cell.

In the rabbit, slight infiltration of the pannicular muscle by mononuclear cells were noted. This minor subcutaneous reaction was uncommon and showed no group related distribution. There was no apparent difference in irritance between ranitidine injection and placebo injection. In the rat, intravenous ranitidine at dose levels of 5.0 and 10.0 mg/kg daily for 15 days and 28 days produced no treatment related changes of biological importance in the hematopoietic system.

In Beagle dogs, intravenous ranitidine injection in doses up to 10 mg/kg/day for 28 and 42 days, produced no drug-related change in circulating erythrocytes or leukocytes and had no adverse effects on the hematopoietic system. No dose related changes were seen in electrocardiograms of Beagle dogs receiving up to 10 mg/kg ranitidine by intravenous injection. At dosage levels of up to 30 mg/kg, administered twice daily to Beagle dogs for 14 or 15 days, intravenous ranitidine injection produced no changes of biological significance in hematology, clinical chemistry or urinalysis.

No changes were observed in the eyes of dogs (specifically the tapetum lucidum) receiving ranitidine in doses up to 30 mg/kg twice daily for 15 days. At intravenous doses above 1.25 mg/kg, ranitidine injection produced immediate and transient reactions in the Beagle dog. The following reactions were typically produced by the administration of 1.25 mg/kg: bloodshot eyes, closing and watering of eyes, defaecation, diarrhea, erythema, flatus, licking of lips, running nose, salivation, subdued behaviour, swallowing, tachycardia, and trembling. The range and severity of the effects was aggravated by increased dosage.

Reproduction Studies (Impairment of Fertility)

Reproduction studies were carried out in the rat and rabbit.

Rats were exposed to ranitidine before and during mating, throughout pregnancy, lactation and during the weaning period. No effects on the reproductive process were seen and there was no evidence of an anti-androgenic effect.

A total of 2,297 fetuses from rats treated with ranitidine were examined. There was no evidence that ranitidine is a rat teratogen. Cleft palates occurred in fetuses from both treatment groups, however, there were significantly more in the control rat population.

A total of 944 fetuses from rabbits treated with ranitidine were examined; no drug-related adverse events or abnormalities in the fetuses were observed.

Rabbits receiving a bolus intravenous injection of ranitidine (10 mg/kg) once daily on gestation days 7-16 exhibited a reduction in weight gain. Their fetuses weighed significantly less than fetuses of untreated controls.

In addition, 12.4% of ranitidine-exposed fetuses had cleft palates. Reanalysis of this and a companion study performed to assess reproducibility demonstrated a lack of data reproducibility. Therefore, the effects observed in the first trial are aberrant, and should not form the basis for maternal or fetal toxicity.

In the subsequent study, no evidence of maternal or fetal toxicity was observed in rabbits dosed with 100 mg/kg ranitidine orally during days 2-29 of pregnancy. The peak plasma levels of ranitidine after a 100 mg/kg oral dose are similar to those obtained one minute after a 10 mg/kg dose administered intravenously (20-25 µg/mL). Therefore, no teratogenic effects of ranitidine have been demonstrated at doses of 10 mg/kg (IV) and 100 mg/kg (Tablets) in rabbits.

Carcinogenicity Studies

There is no evidence that ranitidine is a carcinogen. Long term toxicity and carcinogenicity studies have involved the treatment of 600 mice and 636 rats at doses up to 2,000 mg/kg for two years and 129 weeks respectively and 42 dogs at doses up to 450 mg/kg/day for periods up to one year. These dose levels are far in excess of those to be used therapeutically in man. None of these animals had any intestinal metaplasia. There was no evidence of a tumourigenic effect of ranitidine in any other tissue.

Mutagenesis

Ranitidine is not mutagenic at doses as great as 30 mg/plate in the Ames Assay utilizing *Salmonella typhimurium* (TA 1538, TA 98, TA 100 and TA 1537) or in doses of 9 mg/plate utilizing *Escherichia coli* (WP2 and WP2 uvrA) with or without activation.

Ranitidine at concentrations of 20-30 mg/plate had a weak direct mutagenic action in *S. typhimurium* TA 1535 and at 9 mg/plate in *E. coli* WP67. ZANTAC® was not mutagenic at a concentration of 2 mg/mL in *E. coli* or *S. typhimurium* in the more sensitive Oral Solution microtitre fluctuation assay method. This weak direct mutagenic effect is of no clinical significance; the magnitudes of ranitidine concentration used in these assays are thousands of times greater than that attained therapeutically in human plasma.

The principal metabolites of ranitidine in man were not significantly mutagenic. This conclusion is supported by the following experiment. A test solution obtained by interacting ranitidine (10 mM) and sodium nitrite (40mM) was mutagenic in *S. typhimurium* (TA 1535) but not in *S. typhimurium* (TA 1537) or in *E. coli* (WP67 or WP2 uvrA). This positive result is attributable to the presence of a nitrosonitrolic acid derivative AH 23729, which was mutagenic. When the sodium nitrite concentration was reduced to 15 mM or less, the solution was not mutagenic in any of the test microorganisms. The formation of AH 23729 requires concentrations of nitrous acid far in excess of those encountered in any probable physiological conditions. The other nitrosation products were not mutagenic in any of the microorganisms tested. There is no reason, therefore, for supposing that ranitidine is likely to be mutagenic in animals or man as a consequence of nitrosation in the stomach.

There is no evidence from long term toxicology, carcinogenicity and mutagenicity studies in animals to suggest that ranitidine is likely to have any deleterious effects in man when administered at therapeutic dose levels.

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