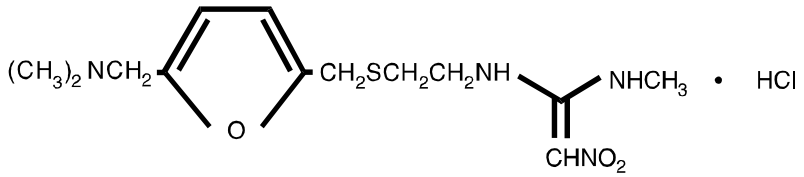
PRODUCT INFORMATION

ZANTAC®
(ranitidine hydrochloride)
Injection

Pharmacy Bulk Package—
Not for Direct Infusion

DESCRIPTION: The active ingredient in ZANTAC Injection is ranitidine hydrochloride (HCl), a histamine H_2-receptor antagonist. Chemically it is N[2-[[[5-[(dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine, hydrochloride. It has the following structure:



The empirical formula is $C_{13}H_{22}N_4O_3S \bullet HCl$, representing a molecular weight of 350.87.

Ranitidine HCl is a white to pale yellow, granular substance that is soluble in water.

ZANTAC Injection is a clear, colorless to yellow, nonpyrogenic liquid. The yellow color of the liquid tends to intensify without adversely affecting potency. The pH of the injection solution is 6.7 to 7.3.

Each 1 mL of aqueous solution contains ranitidine 25 mg (as the hydrochloride); phenol 5 mg as preservative; and 0.96 mg of monobasic potassium phosphate and 2.4 mg of dibasic sodium phosphate as buffers.

A pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture program and are restricted to the preparation of admixtures for intravenous (IV) infusion.

CLINICAL PHARMACOLOGY: ZANTAC is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. ZANTAC does not lower serum Ca++ in hypercalcemic states. ZANTAC is not an anticholinergic agent.
Pharmacokinetics: ***Absorption:*** ZANTAC is absorbed very rapidly after intramuscular (IM) injection. Mean peak levels of 576 ng/mL occur within 15 minutes or less following a 50-mg IM dose. Absorption from IM sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous (IV) administration. Following oral administration, the bioavailability of ZANTAC Tablets is 50%.

Distribution: The volume of distribution is about 1.4 L/kg. Serum protein binding averages 15%.

Metabolism: In humans, the N-oxide is the principal metabolite in the urine; however, this amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool. 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.

Excretion: Following IV injection, approximately 70% of the dose is recovered in the urine as unchanged drug. Renal clearance averages 530 mL/min, with a total clearance of 760 mL/min. The elimination half-life is 2.0 to 2.5 hours.

Four patients with clinically significant renal function impairment (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

Geriatrics: The plasma half-life is prolonged and total clearance is reduced in the elderly population due to a decrease in renal function. The elimination half-life is 3.1 hours (see PRECAUTIONS: Geriatric Use and DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients with Impaired Renal Function).

Pediatrics: There are no significant differences in the pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy adults when correction is made for body weight. The pharmacokinetics of ZANTAC in pediatric patients are summarized in Table 1.

Table 1: Ranitidine Pharmacokinetics in Pediatric Patients Following IV Dosing

Population (age)	n	Dose (mg/kg)	$T_{½}$ (hours)	Vd (L/kg)	CLp (mL/min/kg)
Peptic ulcer disease					
(<6 years)	6	1.25 or 2.5	2.2	1.29	11.41
(6 – 11.9 years)	11	1.25 or 2.5	2.1	1.14	8.96
(>12 years)	6	1.25 or 2.5	1.7	0.98	9.89
Adults	6	2.5	1.9	1.04	8.77
Peptic ulcer disease (3.5 – 16 years)	12	0.13 – 0.80	1.8	2.3	795 mL/min/1.73/m^2
Children in intensive care (1 day – 12.6 years)	17	1.0	2.4	2	11.7
Neonates receiving ECMO	12	2	6.6	1.8	4.3

$T_{½}$ = Terminal half-life; CLp = Plasma clearance of ranitidine.
ECMO = extracorporeal membrane oxygenation.

Plasma clearance in neonatal patients (less than 1 month of age) receiving ECMO was considerably lower (3 to 4 mL/min/kg) than observed in children or adults. The elimination half-life in neonates averaged 6.6 hours as compared to approximately 2 hours in adults and pediatric patients.

Pharmacodynamics: Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following single IV or IM 50-mg doses, serum concentrations of ZANTAC are in this range for 6 to 8 hours.

Antisecretory Activity: ***1. Effects on Acid Secretion:*** ZANTAC Injection inhibits basal gastric acid secretion as well as gastric acid secretion stimulated by betazole and pentagastrin, as shown in Table 2.

Table 2: Effect of Intravenous ZANTAC on Gastric Acid Secretion

	Time After Dose, h	% Inhibition of Gastric Acid Output by Intravenous Dose, mg		
		20 mg	60 mg	100 mg
Betazole	Up to 2	93	99	99
Pentagastrin	Up to 3	47	66	77

In a group of 10 known hypersecretors, ranitidine plasma levels of 71, 180, and 376 ng/mL inhibited basal acid secretion by 76%, 90%, and 99.5%, respectively.

It appears that basal- and betazole-stimulated secretions are most sensitive to inhibition by ZANTAC, while pentagastrin-stimulated secretion is more difficult to suppress.

2. Effects on Other Gastrointestinal Secretions:

Pepsin: ZANTAC does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: ZANTAC has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: ZANTAC has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:

a. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.

b. Prolactin levels—no effect in recommended oral or intravenous dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.

c. Other pituitary hormones—no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.

d. No change in cortisol, aldosterone, androgen, or estrogen levels.

e. No antiandrogenic action.

f. No effect on count, motility, or morphology of sperm.

Pediatrics: The ranitidine concentration necessary to suppress basal acid secretion by at least 90% has been reported to be 40 to 60 ng/mL in pediatric patients with duodenal or gastric ulcers.

In a study of 20 critically ill pediatric patients receiving ranitidine IV at 1 mg/kg every 6 hours, 10 patients with a baseline pH≥4 maintained this baseline throughout the study. Eight of the remaining 10 patients with a baseline of pH≤2 achieved pH≥4 throughout varying periods after dosing. It should be noted, however, that because these pharmacodynamic parameters were assessed in critically ill pediatric patients, the data should be interpreted with caution when dosing recommendations are made for a less seriously ill pediatric population.

In another small study of neonatal patients (n = 5) receiving ECMO, gastric pH<4 pretreatment increased to >4 after a 2 mg/kg dose and remained above 4 for at least 15 hours.

Clinical Trials: ***Active Duodenal Ulcer:*** In a multicenter, double-blind, controlled, US study of endoscopically diagnosed duodenal ulcers, earlier healing was seen in the patients treated with oral ZANTAC as shown in Table 3.

Table 3: Duodenal Ulcer Patient Healing Rates

	Oral ZANTAC*		Oral Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	195	69/182 (38%)†	188	31/164 (19%)
Week 4		137/187 (73%)†		76/168 (45%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$P<0.0001$.

In these studies, patients treated with oral ZANTAC reported a reduction in both daytime and nocturnal pain, and they also consumed less antacid than the placebo-treated patients.

Table 4: Mean Daily Doses of Antacid

	Ulcer Healed	Ulcer Not Healed
Oral ZANTAC	0.06	0.71
Oral placebo	0.71	1.43

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome, systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative, "short-gut" syndrome, idiopathic). Use of oral ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

In a retrospective review of 52 Zollinger-Ellison patients given ZANTAC as a continuous IV infusion for up to 15 days, no patients developed complications of acid-peptic disease such as bleeding or perforation. Acid output was controlled to ≤10 mEq/h.

INDICATIONS AND USAGE: ZANTAC Injection is indicated in some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or as an alternative to the oral dosage form for short-term use in patients who are unable to take oral medication.

CONTRAINDICATIONS: ZANTAC Injection is contraindicated for patients known to have hypersensitivity to the drug.

PRECAUTIONS:
General: 1. Symptomatic response to therapy with ZANTAC does not preclude the presence of gastric malignancy.

2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function (see DOSAGE AND ADMINISTRATION). Caution should be observed in patients with hepatic dysfunction since ZANTAC is metabolized in the liver.

3. In controlled studies in normal volunteers, elevations in SGPT have been observed when H_2-antagonists have been administered intravenously at greater than recommended dosages for 5 days or longer. Therefore, it seems prudent in patients receiving IV ranitidine at dosages ≥100 mg q.i.d. for periods of 5 days or longer to monitor SGPT daily (from day 5) for the remainder of IV therapy.

4. 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 (see DOSAGE AND ADMINISTRATION).

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

Laboratory Tests: False-positive tests for urine protein with MULTISTIX® may occur during therapy with ZANTAC, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although ZANTAC has been reported to bind weakly to cytochrome P-450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P-450–linked oxygenase enzymes in the liver. However, there have been isolated reports of drug interactions that suggest that ZANTAC may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

Increased or decreased prothrombin times have been reported during concurrent use of ranitidine and warfarin. However, in human pharmacokinetic studies with dosages of ranitidine up to 400 mg/day, no interaction occurred; ranitidine had no effect on warfarin clearance or prothrombin time. The possibility of an interaction with warfarin at dosages of ranitidine higher than 400 mg/day has not been investigated.

In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were higher during b.i.d. dosing of ranitidine than triazolam given alone. The mean area under the triazolam concentration-time curve (AUC) values in 18- to 60-year-old subjects were 10% and 28% higher following administration of 75-mg and 150-mg ranitidine tablets, respectively, than triazolam given alone. In subjects older than 60 years of age, the mean AUC values were approximately 30% higher following administration of 75-mg and 150-mg ranitidine tablets. It appears that there were no changes in pharmacokinetics of triazolam and α-hydroxytriazolam, a major metabolite, and in their elimination. Reduced gastric acidity due to ranitidine may have resulted in an increase in the availability of triazolam. The clinical significance of this triazolam and ranitidine pharmacokinetic interaction is unknown.

Carcinogenesis, Mutagenesis, Impairment of Fertility: There was no indication of tumorigenic or carcinogenic effects in life-span studies in mice and rats at oral dosages up to 2000 mg/kg per day.

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays.

In a dominant lethal assay, a single oral dose of 1000 mg/kg to male rats was without effect on the outcome of two matings per week for the next 9 weeks.

Pregnancy: ***Teratogenic Effects:*** Pregnancy Category B*:* Reproduction studies have been performed in rats and rabbits at oral doses up to 160 times the human oral dose and have revealed no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies

are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: ZANTAC is secreted in human milk. Caution should be exercised when ZANTAC is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of ZANTAC Injection have been established in the age-group of 1 month to 16 years for the treatment of duodenal ulcer. Use of ZANTAC in this age-group is supported by adequate and well-controlled studies in adults, as well as additional pharmacokinetic data in pediatric patients, and an analysis of the published literature.

Safety and effectiveness in pediatric patients for the treatment of pathological hypersecretory conditions have not been established.

Limited data in neonatal patients (less than one month of age) receiving ECMO suggest that ZANTAC may be useful and safe for increasing gastric pH for patients at risk of gastrointestinal hemorrhage.

Geriatric Use: Clinical studies of ZANTAC Injection did not include sufficient numbers of subjects aged 65 and over to determine whether they responded differently from younger subjects. However, in clinical studies of oral formulations of ZANTAC**,** of the total number of subjects enrolled in US and foreign controlled clinical trials, for which there were subgroup analyses, 4197 were 65 and over, while 899 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out**.**

This drug is known to be substantially excreted by the kidney and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Geriatric Use and DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients with Impaired Renal Function).

ADVERSE REACTIONS: Transient pain at the site of IM injection has been reported. Transient local burning or itching has been reported with IV administration of ZANTAC.

The following have been reported as events in clinical trials or in the routine management of patients treated with oral or parenteral ZANTAC. The relationship to therapy with ZANTAC has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of ZANTAC.

Central Nervous System: Rarely, malaise, dizziness, somnolence, insomnia, and vertigo. Rare cases of reversible mental confusion, agitation, depression, and hallucinations have been reported, predominantly in severely ill elderly patients. Rare cases of reversible blurred vision suggestive of a change in accommodation have been reported. Rare reports of reversible involuntary motor disturbances have been received.

Cardiovascular: As with other H_2-blockers, rare reports of arrhythmias such as tachycardia, bradycardia, asystole, atrioventricular block, and premature ventricular beats.

Gastrointestinal: Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, and rare reports of pancreatitis.

Hepatic: In normal volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects

receiving 50 mg q.i.d. intravenously for 5 days. There have been occasional reports of hepatocellular, cholestatic, or mixed hepatitis, with or without jaundice. In such circumstances, ranitidine should be immediately discontinued. These events are usually reversible, but in rare circumstances death has occurred. Rare cases of hepatic failure have also been reported.
Musculoskeletal: Rare reports of arthralgias and myalgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic anemia and exceedingly rare cases of acquired immune hemolytic anemia have been reported.
Endocrine: Controlled studies in animals and humans have shown no stimulation of any pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving ZANTAC, but the incidence did not differ from that in the general population.
Integumentary: Rash, including rare cases of erythema multiforme. Rare cases of alopecia and vasculitis.
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

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 REACTIONS). In addition, abnormalities of gait and hypotension have been reported.

When overdosage occurs, clinical monitoring and supportive therapy should be employed.

Studies in dogs receiving dosages of ZANTAC in excess of 225 mg/kg per day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1000 mg/kg in mice and rats were not lethal. Intravenous LD_{50} values in mice and rats were 77 and 83 mg/kg, respectively.

DOSAGE AND ADMINISTRATION:
Parenteral Administration: In some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers, or in patients who are unable to take oral medication, ZANTAC Injection may be administered parenterally according to the following recommendations:

Intramuscular Injection: 50 mg (2 mL) every 6 to 8 hours. (No dilution necessary.)

Intermittent Intravenous Injection:

a. Intermittent Bolus: 50 mg (2 mL) every 6 to 8 hours. Dilute ZANTAC Injection, 50 mg, in 0.9% sodium chloride injection or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/mL (20 mL). Inject at a rate no greater than 4 mL/min (5 minutes).

b. Intermittent Infusion: 50 mg (2 mL) every 6 to 8 hours. Dilute ZANTAC Injection, 50 mg, in 5% dextrose injection or other compatible IV solution (see Stability) to a concentration no greater than 0.5 mg/mL (100 mL). Infuse at a rate no greater than 5 to 7 mL/min (15 to 20 minutes).

In some patients it may be necessary to increase dosage. When this is necessary, the increases should be made by more frequent administration of the dose, but generally should not exceed 400 mg/day.

Continuous Intravenous Infusion: Add ZANTAC Injection to 5% dextrose injection or other compatible IV solution (see Stability). Deliver at a rate of 6.25 mg/h (e.g., 150 mg [6 mL] of ZANTAC Injection in 250 mL of 5% dextrose injection at 10.7 mL/h).

For Zollinger-Ellison patients, dilute ZANTAC Injection in 5% dextrose injection or other compatible IV solution (see Stability) to a concentration no greater than 2.5 mg/mL. Start the infusion at a rate of 1.0 mg/kg per hour. If after 4 hours either a measured gastric acid output is >10 mEq/h or the patient becomes symptomatic, the dose should be adjusted upward in 0.5-mg/kg per hour increments, and the acid output should be remeasured. Dosages up to 2.5 mg/kg per hour and infusion rates as high as 220 mg/h have been used.

Pediatric Use: While limited data exist on the administration of IV ranitidine to children, the recommended dose in pediatric patients is for a total daily dose of 2 to 4 mg/kg, to be divided and administered every 6 to 8 hours, up to a maximum of 50 mg given every 6 to 8 hours. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients. Limited data in neonatal patients (less than one month of age) receiving ECMO have shown that a dose of 2 mg/kg is usually sufficient to increase gastric pH to >4 for at least 15 hours. Therefore, doses of 2 mg/kg given every 12 to 24 hours or as a continuous infusion should be considered.

Dosage Adjustment for Patients With Impaired Renal Function: The administration of ranitidine as a continuous infusion has not been evaluated in patients with impaired renal function. On the basis of experience with a group of subjects with severely impaired renal function treated with ZANTAC, the recommended dosage in patients with a creatinine clearance <50 mL/min is 50 mg every 18 to 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

Elderly patients are more likely to have decreased renal function, therefore caution should be exercised in dose selection, and it may be useful to monitor renal function (see CLINICAL PHARMACOLOGY: Pharmacokinetics: Geriatric Use and PRECAUTIONS: Geriatric Use).

Stability: Undiluted, ZANTAC Injection tends to exhibit a yellow color that may intensify over time without adversely affecting potency. ZANTAC Injection is stable for 48 hours at room temperature when added to or diluted with most commonly used IV solutions, e.g., 0.9% sodium chloride injection, 5% dextrose injection, 10% dextrose injection, lactated ringer's injection, or 5% sodium bicarbonate injection.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

Directions for Dispensing: ***Pharmacy Bulk Package—Not for Direct Infusion:*** The pharmacy bulk package is for use in a pharmacy admixture service only under a laminar flow hood. The closure should be penetrated only once with a sterile transfer set or other sterile dispensing device, which allows measured distribution of the contents, and the contents dispensed in aliquots using aseptic technique. CONTENTS SHOULD BE USED AS SOON AS POSSIBLE FOLLOWING INITIAL CLOSURE PUNCTURE. DISCARD ANY UNUSED PORTION

WITHIN 24 HOURS OF FIRST ENTRY. Following closure puncture, container should be maintained below 30°C (86°F) under a laminar flow hood until contents are dispensed.

HOW SUPPLIED: ZANTAC Injection, 25 mg/mL, containing phenol 0.5% as preservative, in a 40-mL pharmacy bulk package (NDC 0173-0363-00).

Store between 4° and 30°C (39° and 86°F). Protect from light. Store vial in carton until time of use.

GlaxoSmithKline
Research Triangle Park, NC 27709

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