PRESCRIBING INFORMATION

ZANTAC® 150
(ranitidine hydrochloride)
Tablets, USP

ZANTAC® 300
(ranitidine hydrochloride)
Tablets, USP

ZANTAC® 25
(ranitidine hydrochloride effervescent)
EFFERdose® Tablets

ZANTAC® 150
(ranitidine hydrochloride effervescent)
EFFERdose® Tablets

ZANTAC®
(ranitidine hydrochloride)
Syrup, USP

DESCRIPTION

The active ingredient in ZANTAC 150 Tablets, ZANTAC 300 Tablets, ZANTAC 25 EFFERdose Tablets, ZANTAC 150 EFFERdose Tablets, and ZANTAC Syrup is ranitidine hydrochloride (HCl), USP, 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, HCl. It has the following structure:

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

Ranitidine HCl is a white to pale yellow, granular substance that is soluble in water. It has a slightly bitter taste and sulfurlike odor.

Each ZANTAC 150 Tablet for oral administration contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine. Each tablet also contains the inactive ingredients FD&C Yellow No. 6 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

Each ZANTAC 300 Tablet for oral administration contains 336 mg of ranitidine HCl equivalent to 300 mg of ranitidine. Each tablet also contains the inactive ingredients

croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

ZANTAC 25 EFFERdose Tablets for oral administration is an effervescent formulation of ranitidine that must be dissolved in water before use. Each individual tablet contains 28 mg of ranitidine HCl equivalent to 25 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate. Each tablet also contains sodium benzoate. The total sodium content of each tablet is 30.52 mg (1.33 mEq) per 25 mg of ranitidine.

ZANTAC 150 EFFERdose Tablets for oral administration is an effervescent formulation of ranitidine that must be dissolved in water before use. Each individual tablet contains 168 mg of ranitidine HCl equivalent to 150 mg of ranitidine and the following inactive ingredients: aspartame, monosodium citrate anhydrous, povidone, and sodium bicarbonate. Each tablet also contains sodium benzoate. The total sodium content of each tablet is 183.12 mg (7.96 mEq) per 150 mg of ranitidine.

Each 1 mL of ZANTAC Syrup contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine. ZANTAC Syrup also contains the inactive ingredients alcohol (7.5%), butylparaben, dibasic sodium phosphate, hypromellose, peppermint flavor, monobasic potassium phosphate, propylparaben, purified water, saccharin sodium, sodium chloride, and sorbitol.

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 50% absorbed after oral administration, compared to an intravenous (IV) injection with mean peak levels of 440 to 545 ng/mL occurring 2 to 3 hours after a 150-mg dose. The syrup and EFFERdose formulations are bioequivalent to the tablets. Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC, probably by delaying gastric emptying and transit time. In one study, simultaneous administration of high-potency antacid (150 mmol) in fasting subjects has been reported to decrease the absorption of ZANTAC.

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: 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 410 mL/min, indicating active tubular excretion. The elimination half-life is 2.5 to 3 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 to 4 hours. Peak levels average 526 ng/mL following a 150-mg twice daily dose and occur in about 3 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 average bioavailability of ranitidine given orally to pediatric patients is 48% which is comparable to the bioavailability of ranitidine in the adult population. All other pharmacokinetic parameter values ($t_{1/2}$, Vd, and CL) are similar to those observed with intravenous ranitidine use in pediatric patients. Estimates of C_{max} and T_{max} are displayed in Table 1.

Table 1. Ranitidine Pharmacokinetics in Pediatric Patients Following Oral Dosing

Population (age)	n	Dosage Form (dose)	C_{max} (ng/mL)	T_{max} (hours)
Gastric or duodenal ulcer (3.5 to 16 years)	12	Tablets (1 to 2 mg/kg)	54 to 492	2.0
Otherwise healthy requiring ZANTAC (0.7 to 14 years, Single dose)	10	Syrup (2 mg/kg)	244	1.61
Otherwise healthy requiring ZANTAC (0.7 to 14 years, Multiple dose)	10	Syrup (2 mg/kg)	320	1.66

Plasma clearance measured in 2 neonatal patients (less than 1 month of age) was considerably lower (3 mL/min/kg) than children or adults and is likely due to reduced renal function observed in this population (see PRECAUTIONS: Pediatric Use and DOSAGE AND ADMINISTRATION: Pediatric Use).

Pharmacodynamics: 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 ZANTAC are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

In a pharmacodynamic comparison of the EFFERdose with the ZANTAC Tablets, during the first hour after administration, the EFFERdose tablet formulation gave a significantly higher intragastric pH, by approximately 1 pH unit, compared to the ZANTAC tablets.

Antisecretory Activity: 1. Effects on Acid Secretion: ZANTAC inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in Table 2.

Table 2. Effect of Oral ZANTAC on Gastric Acid Secretion

	Time After Dose, h	% Inhibition of Gastric Acid Output by Dose, mg			
		75-80	100	150	200
Basal	Up to 4		99	95	
Nocturnal	Up to 13	95	96	92	
Betazole	Up to 3		97	99	
Pentagastrin	Up to 5	58	72	72	80
Meal	Up to 3		73	79	95

It appears that basal-, nocturnal-, and betazole-stimulated secretions are most sensitive to inhibition by ZANTAC, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are more difficult to suppress.

2. Effects on Other Gastrointestinal Secretions:

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

Intrinsic Factor: Oral 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:

1. Gastric bacterial flora—increase in nitrate-reducing organisms, significance not known.
2. Prolactin levels—no effect in recommended oral or intravenous (IV) dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.
3. Other pituitary hormones—no effect on serum gonadotropins, TSH, or GH. Possible impairment of vasopressin release.
4. No change in cortisol, aldosterone, androgen, or estrogen levels.
5. No antiandrogenic action.
6. No effect on count, motility, or morphology of sperm.

Pediatrics: Oral doses of 6 to 10 mg/kg per day in 2 or 3 divided doses maintain gastric pH>4 throughout most of the dosing interval.

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 ZANTAC as shown in Table 3.

Table 3. Duodenal Ulcer Patient Healing Rates

	ZANTAC*		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 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
ZANTAC	0.06	0.71
Placebo	0.71	1.43

Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg h.s. (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to 300 mg h.s. (92% versus 87%, respectively).

Studies have been limited to short-term treatment of acute duodenal ulcer. Patients whose ulcers healed during therapy had recurrences of ulcers at the usual rates.

Maintenance Therapy in Duodenal Ulcer: Ranitidine has been found to be effective as maintenance therapy for patients following healing of acute duodenal ulcers. In 2 independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers observed was significantly less in patients treated with ZANTAC (150 mg h.s.) than in patients treated with placebo over a 12-month period.

Table 5. Duodenal Ulcer Prevalence

Double-Blind, Multicenter, Placebo-Controlled Trials					
Multicenter Trial	Drug	Duodenal Ulcer Prevalence			No. of Patients
		0-4 Months	0-8 Months	0-12 Months	
USA	RAN	20%*	24%*	35%*	138
	PLC	44%	54%	59%	139
Foreign	RAN	12%*	21%*	28%*	174
	PLC	56%	64%	68%	165

% = Life table estimate.
* = $P<0.05$ (ZANTAC versus comparator).
RAN = ranitidine (ZANTAC).
PLC = placebo.

As with other H_2-antagonists, the factors responsible for the significant reduction in the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid healing of ulcers that may occur during maintenance therapy, or both.

Gastric Ulcer: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, earlier healing was seen in the patients treated with ZANTAC as shown in Table 6.

Table 6. Gastric Ulcer Patient Healing Rates

	ZANTAC*		Placebo*	
	Number Entered	Healed/ Evaluable	Number Entered	Healed/ Evaluable
Outpatients				
Week 2	92	16/83 (19%)	94	10/83 (12%)
Week 6		50/73 (68%)†		35/69 (51%)

*All patients were permitted p.r.n. antacids for relief of pain.
†$P = 0.009$.

In this multicenter trial, significantly more patients treated with ZANTAC became pain free during therapy.

Maintenance of Healing of Gastric Ulcers: In 2 multicenter, double-blind, randomized, placebo-controlled, 12-month trials conducted in patients whose gastric ulcers had been

previously healed, ZANTAC 150 mg h.s. was significantly more effective than placebo in maintaining healing of gastric ulcers.

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 ZANTAC was followed by healing of ulcers in 8 of 19 (42%) patients who were intractable to previous therapy.

Gastroesophageal Reflux Disease (GERD): In 2 multicenter, double-blind, placebo-controlled, 6-week trials performed in the United States and Europe, ZANTAC 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other symptoms associated with GERD. Ranitidine-treated patients consumed significantly less antacid than did placebo-treated patients.

The US trial indicated that ZANTAC 150 mg b.i.d. significantly reduced the frequency of heartburn attacks and severity of heartburn pain within 1 to 2 weeks after starting therapy. The improvement was maintained throughout the 6-week trial period. Moreover, patient response rates demonstrated that the effect on heartburn extends through both the day and night time periods.

In 2 additional US multicenter, double-blind, placebo-controlled, 2-week trials, ZANTAC 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy and a reduction in the frequency of severity of heartburn. In these trials, ZANTAC EFFERdose Tablets were shown to provide heartburn relief within 45 minutes of dosing.

Erosive Esophagitis: In 2 multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ZANTAC 150 mg q.i.d. was significantly more effective than placebo in healing endoscopically diagnosed erosive esophagitis and in relieving associated heartburn. The erosive esophagitis healing rates were as follows:

Table 7. Erosive Esophagitis Patient Healing Rates

	Healed/Evaluable	
	Placebo* n = 229	ZANTAC 150 mg q.i.d.* n = 215
Week 4	43/198 (22%)	96/206 (47%)†
Week 8	63/176 (36%)	142/200 (71%)†
Week 12	92/159 (58%)	162/192 (84%)†

*All patients were permitted p.r.n. antacids for relief of pain.
†$P<0.001$ versus placebo.

No additional benefit in healing of esophagitis or in relief of heartburn was seen with a ranitidine dose of 300 mg q.i.d.

Maintenance of Healing of Erosive Esophagitis: In 2 multicenter, double-blind, randomized, placebo-controlled, 48-week trials conducted in patients whose erosive esophagitis had been previously healed, ZANTAC 150 mg b.i.d. was significantly more effective than placebo in maintaining healing of erosive esophagitis.

INDICATIONS AND USAGE

ZANTAC is indicated in:

1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks. Studies available to date have not assessed the safety of ranitidine in uncomplicated duodenal ulcer for periods of more than 8 weeks.
2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of acute ulcers. No placebo-controlled comparative studies have been carried out for periods of longer than 1 year.
3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison syndrome and systemic mastocytosis).
4. Short-term treatment of active, benign gastric ulcer. Most patients heal within 6 weeks and the usefulness of further treatment has not been demonstrated. Studies available to date have not assessed the safety of ranitidine in uncomplicated, benign gastric ulcer for periods of more than 6 weeks.
5. Maintenance therapy for gastric ulcer patients at reduced dosage after healing of acute ulcers. Placebo-controlled studies have been carried out for 1 year.
6. Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after starting therapy with ZANTAC 150 mg b.i.d.
7. Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of heartburn commonly occurs within 24 hours of therapy initiation with ZANTAC 150 mg q.i.d.
8. Maintenance of healing of erosive esophagitis. Placebo-controlled trials have been carried out for 48 weeks.

Concomitant antacids should be given as needed for pain relief to patients with active duodenal ulcer; active, benign gastric ulcer; hypersecretory states; GERD; and erosive esophagitis.

CONTRAINDICATIONS

ZANTAC is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients (see PRECAUTIONS).

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. 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.

Information for Patients: ***Phenylketonurics:*** ZANTAC 25 EFFERdose Tablets contain phenylalanine 2.81 mg per 25 mg of ranitidine. ZANTAC 150 EFFERdose Tablets contain phenylalanine 16.84 mg per 150 mg of ranitidine. ZANTAC EFFERdose Tablets should not be chewed, swallowed whole, or dissolved on the tongue.

Laboratory Tests: False-positive tests for urine protein with MULTISTIX® may occur during ZANTAC therapy, 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 dosages up to 2,000 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 1,000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

Pregnancy: *Teratogenic Effects*: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 160 times the human 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 have been established in the age-group of 1 month to 16 years for the treatment of duodenal and gastric ulcers, gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed duodenal and gastric 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 (see CLINICAL PHARMACOLOGY: Pediatrics and DOSAGE AND ADMINISTRATION: Pediatric Use).

Safety and effectiveness in pediatric patients for the treatment of pathological hypersecretory conditions or the maintenance of healing of erosive esophagitis have not been established.

Safety and effectiveness in neonates (less than 1 month of age) have not been established (see CLINICAL PHARMACOLOGY: Pediatrics).

Geriatric Use: Of the total number of subjects enrolled in US and foreign controlled clinical trials of oral formulations of ZANTAC, for which there were subgroup analyses, 4,197 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: Geriatrics and DOSAGE AND ADMINISTRATION: Dosage Adjustment for Patients With Impaired Renal Function).

ADVERSE REACTIONS

The following have been reported as events in clinical trials or in the routine management of patients treated with 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, atrioventricular block, and premature ventricular beats.

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

Hepatic: 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. 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.

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 man 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.

Respiratory: A large epidemiological study suggested an increased risk of developing pneumonia in current users of histamine-2-receptor antagonists (H_2RAs) compared to patients who had stopped H_2RA treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07-2.48). However, a causal relationship between use of H_2RAs and pneumonia has not been established.

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 limited experience with overdosage. 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, the usual measures to remove unabsorbed material from the gastrointestinal tract, 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 1,000 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

Active Duodenal Ulcer: The current recommended adult oral dosage of ZANTAC for duodenal ulcer is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL of syrup (4 teaspoonfuls of syrup equivalent to 300 mg of ranitidine) once daily after the evening meal or at bedtime can be used for patients in whom dosing convenience is important. The advantages of one treatment regimen compared to the other in a particular patient population have yet to be demonstrated (see Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that 100 mg twice daily is as effective as the 150-mg dose.

Antacid should be given as needed for relief of pain (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Maintenance of Healing of Duodenal Ulcers: The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at bedtime.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome): The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer ZANTAC 150-mg doses more frequently. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated. Dosages up to 6 g/day have been employed in patients with severe disease.

Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

Maintenance of Healing of Gastric Ulcers: The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at bedtime.

GERD: The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) 4 times a day.

Maintenance of Healing of Erosive Esophagitis: The current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

Pediatric Use: The safety and effectiveness of ZANTAC have been established in the age-group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of ZANTAC in neonatal patients (less than 1 month of age) to make dosing recommendations.

The following 3 subsections provide dosing information for each of the pediatric indications. Also, see the subsection on Preparation of ZANTAC 25 EFFERdose Tablets, below.

Treatment of Duodenal and Gastric Ulcers: The recommended oral dose for the treatment of active duodenal and gastric ulcers is 2 to 4 mg/kg twice daily to a maximum of 300 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

Maintenance of Healing of Duodenal and Gastric Ulcers: The recommended oral dose for the maintenance of healing of duodenal and gastric ulcers is 2 to 4 mg/kg once daily to a maximum of 150 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

Treatment of GERD and Erosive Esophagitis: Although limited data exist for these conditions in pediatric patients, published literature supports a dosage of 5 to 10 mg/kg per day, usually given as 2 divided doses.

Dosage Adjustment for 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 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) every 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: Geriatrics and PRECAUTIONS: Geriatric Use).

Preparation of ZANTAC 25 EFFERdose Tablets: Tablets should not be chewed, swallowed whole, or dissolved on the tongue. Dissolve 1 tablet in no less than 5 mL (1 teaspoonful) of water in an appropriate measuring cup. Wait until the tablet is completely dissolved before administering the solution to the infant/child. The solution may be administered by medicine dropper or oral syringe for infants.

Preparation of ZANTAC 150 EFFERdose Tablets: Tablets should not be chewed, swallowed whole, or dissolved on the tongue. Dissolve each dose in approximately 6 to 8 oz of water before drinking.

HOW SUPPLIED

ZANTAC 150 Tablets (ranitidine HCl equivalent to 150 mg of ranitidine) are peach, film-coated, 5-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the

other. They are available in bottles of 60 (NDC 0173-0344-42), 180 (NDC 0173-0344-17), and 500 (NDC 0173-0344-14) tablets and unit dose packs of 100 (NDC 0173-0344-47) tablets.

ZANTAC 300 Tablets (ranitidine HCl equivalent to 300 mg of ranitidine) are yellow, film-coated, capsule-shaped tablets embossed with "ZANTAC 300" on one side and "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and 250 (NDC 0173-0393-06) tablets.

Store between 15° and 30°C (59°and 86°F) in a dry place. Protect from light. Replace cap securely after each opening.

ZANTAC 25 EFFERdose Tablets (ranitidine HCl equivalent to 25 mg of ranitidine) are white to pale yellow, round, flat-faced, bevel-edged tablets embossed with “GS” on one side and “25C” on the other side. They are packaged in foil strips and are available in a carton of 60 (NDC 0173-0734-00) tablets.

ZANTAC 150 EFFERdose Tablets (ranitidine HCl equivalent to 150 mg of ranitidine) are white to pale yellow, round, flat-faced, bevel-edged tablets embossed with "ZANTAC 150" on one side and "427" on the other. They are packaged individually in foil and are available in a carton of 60 (NDC 0173-0427-02) tablets.

Store between 2° and 30°C (36° and 86°F).

ZANTAC Syrup, a clear, pale yellow, peppermint-flavored liquid, contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine per 1 mL (75 mg/5 mL) in bottles of 16 fluid ounces (one pint) (NDC 0173-0383-54).

Store between 4° and 25°C (39° and 77°F). Dispense in tight, light-resistant containers as defined in the USP/NF.

GlaxoSmithKline
Research Triangle Park, NC 27709

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