

PRESCRIBING INFORMATION

ZANTAC[®] 150
(ranitidine hydrochloride)
Tablets, USP

ZANTAC[®] 300
(ranitidine hydrochloride)
Tablets, USP

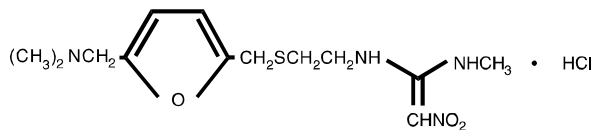
ZANTAC[®] 25
(ranitidine hydrochloride effervescent)
EFFERdose[®] Tablets

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 H₂-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 C₁₃H₂₂N₄O₃·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

37 FD&C Yellow No. 6 Aluminum Lake, hypromellose, magnesium stearate,
38 microcrystalline cellulose, titanium dioxide, triacetin, and yellow iron oxide.

39 Each ZANTAC 300 Tablet for oral administration contains 336 mg of ranitidine HCl
40 equivalent to 300 mg of ranitidine. Each tablet also contains the inactive ingredients
41 croscarmellose sodium, D&C Yellow No. 10 Aluminum Lake, hypromellose, magnesium
42 stearate, microcrystalline cellulose, titanium dioxide, and triacetin.

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

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

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

60

61 **CLINICAL PHARMACOLOGY**

62 ZANTAC is a competitive, reversible inhibitor of the action of histamine at the
63 histamine H₂-receptors, including receptors on the gastric cells. ZANTAC does not lower
64 serum Ca⁺⁺ in hypercalcemic states. ZANTAC is not an anticholinergic agent.

65 **Pharmacokinetics:**

66 **Absorption:** ZANTAC is 50% absorbed after oral administration, compared to an
67 intravenous (IV) injection with mean peak levels of 440 to 545 ng/mL occurring 2 to
68 3 hours after a 150-mg dose. The syrup and EFFERdose formulations are bioequivalent to
69 the tablets. Absorption is not significantly impaired by the administration of food or
70 antacids. Propantheline slightly delays and increases peak blood levels of ZANTAC,
71 probably by delaying gastric emptying and transit time. In one study, simultaneous
72 administration of high-potency antacid (150 mmol) in fasting subjects has been reported
73 to decrease the absorption of ZANTAC.

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

76 **Metabolism:** In humans, the N-oxide is the principal metabolite in the urine; however,
77 this amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the
78 desmethyl ranitidine (1%). The remainder of the administered dose is found in the stool.
79 Studies in patients with hepatic dysfunction (compensated cirrhosis) indicate that there
80 are minor, but clinically insignificant, alterations in ranitidine half-life, distribution,
81 clearance, and bioavailability.

82 **Excretion:** The principal route of excretion is the urine, with approximately 30% of
83 the orally administered dose collected in the urine as unchanged drug in 24 hours. Renal
84 clearance is about 410 mL/min, indicating active tubular excretion. The elimination half-
85 life is 2.5 to 3 hours. Four patients with clinically significant renal function impairment
86 (creatinine clearance 25 to 35 mL/min) administered 50 mg of ranitidine intravenously
87 had an average plasma half-life of 4.8 hours, a ranitidine clearance of 29 mL/min, and a
88 volume of distribution of 1.76 L/kg. In general, these parameters appear to be altered in
89 proportion to creatinine clearance (see DOSAGE AND ADMINISTRATION).

90 **Geriatrics:** The plasma half-life is prolonged and total clearance is reduced in the
91 elderly population due to a decrease in renal function. The elimination half-life is 3 to
92 4 hours. Peak levels average 526 ng/mL following a 150-mg twice daily dose and occur
93 in about 3 hours (see PRECAUTIONS: Geriatric Use and DOSAGE AND
94 ADMINISTRATION: Dosage Adjustment for Patients With Impaired Renal Function).

95 **Pediatrics:** There are no significant differences in the pharmacokinetic parameter
96 values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and healthy
97 adults when correction is made for body weight. The average bioavailability of ranitidine
98 given orally to pediatric patients is 48% which is comparable to the bioavailability of
99 ranitidine in the adult population. All other pharmacokinetic parameter values ($t_{1/2}$, V_d ,
100 and CL) are similar to those observed with intravenous ranitidine use in pediatric patients.
101 Estimates of C_{max} and T_{max} are displayed in Table 1.

102
103

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

104
105
106

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

107 renal function observed in this population (see PRECAUTIONS: Pediatric Use and
108 DOSAGE AND ADMINISTRATION: Pediatric Use).

109 **Pharmacodynamics:** Serum concentrations necessary to inhibit 50% of stimulated
110 gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of
111 150 mg, serum concentrations of ZANTAC are in this range up to 12 hours. However,
112 blood levels bear no consistent relationship to dose or degree of acid inhibition.

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

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

120

121 **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

122

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

126 **2. Effects on Other Gastrointestinal Secretions:**

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

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

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

133 **Other Pharmacologic Actions:**

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

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

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

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

142 *e.* No antiandrogenic action.

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

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

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

149

150 **Table 3. Duodenal Ulcer Patient Healing Rates**

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

151 *All patients were permitted p.r.n. antacids for relief of pain.

152 [†]P<0.0001.

153

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

156

157 **Table 4. Mean Daily Doses of Antacid**

	Ulcer Healed	Ulcer Not Healed
ZANTAC	0.06	0.71
Placebo	0.71	1.43

158

159 Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and
160 300 mg h.s. (85% versus 84%, respectively) during a usual 4-week course of therapy. If
161 patients require extended therapy of 8 weeks, the healing rate may be higher for 150 mg
162 b.i.d. as compared to 300 mg h.s. (92% versus 87%, respectively).

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

165 **Maintenance Therapy in Duodenal Ulcer:** Ranitidine has been found to be effective
166 as maintenance therapy for patients following healing of acute duodenal ulcers. In

167 2 independent, double-blind, multicenter, controlled trials, the number of duodenal ulcers
168 observed was significantly less in patients treated with ZANTAC (150 mg h.s.) than in
169 patients treated with placebo over a 12-month period.

170

171 **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

172 % = Life table estimate.

173 * = $P < 0.05$ (ZANTAC versus comparator).

174 RAN = ranitidine (ZANTAC).

175 PLC = placebo.

176

177 As with other H₂-antagonists, the factors responsible for the significant reduction in
178 the prevalence of duodenal ulcers include prevention of recurrence of ulcers, more rapid
179 healing of ulcers that may occur during maintenance therapy, or both.

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

183

184 **Table 6. Gastric Ulcer Patient Healing Rates**

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

185 *All patients were permitted p.r.n. antacids for relief of pain.

186 [†] $P = 0.009$.

187

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

190 ***Maintenance of Healing of Gastric Ulcers:*** In 2 multicenter, double-blind,
191 randomized, placebo-controlled, 12-month trials conducted in patients whose gastric
192 ulcers had been previously healed, ZANTAC 150 mg h.s. was significantly more effective
193 than placebo in maintaining healing of gastric ulcers.

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

200 ***Gastroesophageal Reflux Disease (GERD):*** In 2 multicenter, double-blind,
201 placebo-controlled, 6-week trials performed in the United States and Europe, ZANTAC
202 150 mg b.i.d. was more effective than placebo for the relief of heartburn and other
203 symptoms associated with GERD. Ranitidine-treated patients consumed significantly less
204 antacid than did placebo-treated patients.

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

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

215 ***Erosive Esophagitis:*** In 2 multicenter, double-blind, randomized, placebo-controlled,
216 12-week trials performed in the United States, ZANTAC 150 mg q.i.d. was significantly
217 more effective than placebo in healing endoscopically diagnosed erosive esophagitis and
218 in relieving associated heartburn. The erosive esophagitis healing rates were as follows:
219

220 **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%) [†]

221 *All patients were permitted p.r.n. antacids for relief of pain.

222 [†]P<0.001 versus placebo.

223

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

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

230

231 **INDICATIONS AND USAGE**

232 ZANTAC is indicated in:

- 233 1. Short-term treatment of active duodenal ulcer. Most patients heal within 4 weeks.
234 Studies available to date have not assessed the safety of ranitidine in uncomplicated
235 duodenal ulcer for periods of more than 8 weeks.
- 236 2. Maintenance therapy for duodenal ulcer patients at reduced dosage after healing of
237 acute ulcers. No placebo-controlled comparative studies have been carried out for
238 periods of longer than 1 year.
- 239 3. The treatment of pathological hypersecretory conditions (e.g., Zollinger-Ellison
240 syndrome and systemic mastocytosis).
- 241 4. Short-term treatment of active, benign gastric ulcer. Most patients heal within
242 6 weeks and the usefulness of further treatment has not been demonstrated. Studies
243 available to date have not assessed the safety of ranitidine in uncomplicated, benign
244 gastric ulcer for periods of more than 6 weeks.
- 245 5. Maintenance therapy for gastric ulcer patients at reduced dosage after healing of acute
246 ulcers. Placebo-controlled studies have been carried out for 1 year.
- 247 6. Treatment of GERD. Symptomatic relief commonly occurs within 24 hours after
248 starting therapy with ZANTAC 150 mg b.i.d.
- 249 7. Treatment of endoscopically diagnosed erosive esophagitis. Symptomatic relief of
250 heartburn commonly occurs within 24 hours of therapy initiation with ZANTAC
251 150 mg q.i.d.

252 8. Maintenance of healing of erosive esophagitis. Placebo-controlled trials have been
253 carried out for 48 weeks.

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

257

258 **CONTRAINDICATIONS**

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

261

262 **PRECAUTIONS**

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

265 2. Since ZANTAC is excreted primarily by the kidney, dosage should be adjusted in
266 patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

267 Caution should be observed in patients with hepatic dysfunction since ZANTAC is
268 metabolized in the liver.

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

272 **Information for Patients: Phenylketonurics:** ZANTAC 25 EFFERdose Tablets contain
273 phenylalanine 2.81 mg per 25 mg of ranitidine. ZANTAC 150 EFFERdose Tablets
274 contain phenylalanine 16.84 mg per 150 mg of ranitidine.

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

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

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

288 In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations
289 were higher during b.i.d. dosing of ranitidine than triazolam given alone. The mean area
290 under the triazolam concentration-time curve (AUC) values in 18- to 60-year-old subjects
291 were 10% and 28% higher following administration of 75-mg and 150-mg ranitidine

292 tablets, respectively, than triazolam given alone. In subjects older than 60 years of age,
293 the mean AUC values were approximately 30% higher following administration of 75-mg
294 and 150-mg ranitidine tablets. It appears that there were no changes in pharmacokinetics
295 of triazolam and α -hydroxytriazolam, a major metabolite, and in their elimination.
296 Reduced gastric acidity due to ranitidine may have resulted in an increase in the
297 availability of triazolam. The clinical significance of this triazolam and ranitidine
298 pharmacokinetic interaction is unknown.

299 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** There was no indication of
300 tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to
301 2,000 mg/kg per day.

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

304 In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without
305 effect on the outcome of 2 matings per week for the next 9 weeks.

306 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
307 performed in rats and rabbits at doses up to 160 times the human dose and have revealed
308 no evidence of impaired fertility or harm to the fetus due to ZANTAC. There are,
309 however, no adequate and well-controlled studies in pregnant women. Because animal
310 reproduction studies are not always predictive of human response, this drug should be
311 used during pregnancy only if clearly needed.

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

314 **Pediatric Use:** The safety and effectiveness of ZANTAC have been established in the
315 age-group of 1 month to 16 years for the treatment of duodenal and gastric ulcers,
316 gastroesophageal reflux disease and erosive esophagitis, and the maintenance of healed
317 duodenal and gastric ulcer. Use of ZANTAC in this age-group is supported by adequate
318 and well-controlled studies in adults, as well as additional pharmacokinetic data in
319 pediatric patients and an analysis of the published literature (see CLINICAL
320 PHARMACOLOGY: Pediatrics and DOSAGE AND ADMINISTRATION: Pediatric
321 Use).

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

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

327 **Geriatric Use:** Of the total number of subjects enrolled in US and foreign controlled
328 clinical trials of oral formulations of ZANTAC, for which there were subgroup analyses,
329 4,197 were 65 and over, while 899 were 75 and over. No overall differences in safety or
330 effectiveness were observed between these subjects and younger subjects, and other
331 reported clinical experience has not identified differences in responses between the

332 elderly and younger patients, but greater sensitivity of some older individuals cannot be
333 ruled out.

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

340

341 **ADVERSE REACTIONS**

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

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

351 **Cardiovascular:** As with other H₂-blockers, rare reports of arrhythmias such as
352 tachycardia, bradycardia, atrioventricular block, and premature ventricular beats.

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

355 **Hepatic:** There have been occasional reports of hepatocellular, cholestatic, or mixed
356 hepatitis, with or without jaundice. In such circumstances, ranitidine should be
357 immediately discontinued. These events are usually reversible, but in rare circumstances
358 death has occurred. Rare cases of hepatic failure have also been reported. In normal
359 volunteers, SGPT values were increased to at least twice the pretreatment levels in 6 of
360 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 24 subjects
361 receiving 50 mg q.i.d. intravenously for 5 days.

362 **Musculoskeletal:** Rare reports of arthralgias and myalgias.

363 **Hematologic:** Blood count changes (leukopenia, granulocytopenia, and
364 thrombocytopenia) have occurred in a few patients. These were usually reversible. Rare
365 cases of agranulocytosis, pancytopenia, sometimes with marrow hypoplasia, and aplastic
366 anemia and exceedingly rare cases of acquired immune hemolytic anemia have been
367 reported.

368 **Endocrine:** Controlled studies in animals and man have shown no stimulation of any
369 pituitary hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced
370 gynecomastia and impotence in hypersecretory patients have resolved when ZANTAC
371 has been substituted. However, occasional cases of gynecomastia, impotence, and loss of

372 libido have been reported in male patients receiving ZANTAC, but the incidence did not
373 differ from that in the general population.

374 **Integumentary:** Rash, including rare cases of erythema multiforme. Rare cases of
375 alopecia and vasculitis.

376 **Other:** Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash,
377 eosinophilia), anaphylaxis, angioneurotic edema, and small increases in serum creatinine.

378

379 **OVERDOSAGE**

380 There has been limited experience with overdosage. Reported acute ingestions of up to
381 18 g orally have been associated with transient adverse effects similar to those
382 encountered in normal clinical experience (see ADVERSE REACTIONS). In addition,
383 abnormalities of gait and hypotension have been reported.

384 When overdosage occurs, the usual measures to remove unabsorbed material from the
385 gastrointestinal tract, clinical monitoring, and supportive therapy should be employed.

386 Studies in dogs receiving dosages of ZANTAC in excess of 225 mg/kg per day have
387 shown muscular tremors, vomiting, and rapid respiration. Single oral doses of
388 1,000 mg/kg in mice and rats were not lethal. Intravenous LD₅₀ values in mice and rats
389 were 77 and 83 mg/kg, respectively.

390

391 **DOSAGE AND ADMINISTRATION**

392 **Active Duodenal Ulcer:** The current recommended adult oral dosage of ZANTAC for
393 duodenal ulcer is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to
394 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL of syrup
395 (4 teaspoonfuls of syrup equivalent to 300 mg of ranitidine) once daily after the evening
396 meal or at bedtime can be used for patients in whom dosing convenience is important.
397 The advantages of one treatment regimen compared to the other in a particular patient
398 population have yet to be demonstrated (see Clinical Trials: *Active Duodenal Ulcer*).
399 Smaller doses have been shown to be equally effective in inhibiting gastric acid secretion
400 in US studies, and several foreign trials have shown that 100 mg twice daily is as
401 effective as the 150-mg dose.

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

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

407 **Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):** The
408 current recommended adult oral dosage is 150 mg or 10 mL of syrup (2 teaspoonfuls of
409 syrup equivalent to 150 mg of ranitidine) twice a day. In some patients it may be
410 necessary to administer ZANTAC 150-mg doses more frequently. Dosages should be

411 adjusted to individual patient needs, and should continue as long as clinically indicated.
412 Dosages up to 6 g/day have been employed in patients with severe disease.

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

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

418 **GERD:** The current recommended adult oral dosage is 150 mg or 10 mL of syrup
419 (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

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

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

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

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

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

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

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

443 **Dosage Adjustment for Patients With Impaired Renal Function:** On the basis of
444 experience with a group of subjects with severely impaired renal function treated with
445 ZANTAC, the recommended dosage in patients with a creatinine clearance <50 mL/min
446 is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine)
447 every 24 hours. Should the patient's condition require, the frequency of dosing may be
448 increased to every 12 hours or even further with caution. Hemodialysis reduces the level
449 of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing
450 of a scheduled dose coincides with the end of hemodialysis.

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

455 **Preparation of ZANTAC 25 EFFERdose Tablets:** Dissolve 1 tablet in no less than
456 5 mL (1 teaspoonful) of water in an appropriate measuring cup. Wait until the tablet is
457 completely dissolved before administering the solution to the infant/child. The solution
458 may be administered by medicine dropper for infants.

459 **Preparation of ZANTAC 150 EFFERdose Tablets:** Dissolve each dose in
460 approximately 6 to 8 oz of water before drinking.

461

462 **HOW SUPPLIED**

463 ZANTAC 150 Tablets (ranitidine HCl equivalent to 150 mg of ranitidine) are peach,
464 film-coated, 5-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on
465 the other. They are available in bottles of 60 (NDC 0173-0344-42), 180 (NDC 0173-
466 0344-17), 500 (NDC 0173-0344-14), and 1,000 (NDC 0173-0344-12) tablets and unit
467 dose packs of 100 (NDC 0173-0344-47) tablets.

468 ZANTAC 300 Tablets (ranitidine HCl equivalent to 300 mg of ranitidine) are yellow,
469 film-coated, capsule-shaped tablets embossed with "ZANTAC 300" on one side and
470 "Glaxo" on the other. They are available in bottles of 30 (NDC 0173-0393-40) and 250
471 (NDC 0173-0393-06) tablets and unit dose packs of 100 (NDC 0173-0393-47) tablets.

472 **Store between 15° and 30°C (59° and 86°F) in a dry place. Protect from light.**

473 **Replace cap securely after each opening.**

474 ZANTAC 25 EFFERdose Tablets (ranitidine HCl equivalent to 25 mg of ranitidine)
475 are white to pale yellow, round, flat-faced, bevel-edged tablets embossed with "GS" on
476 one side and "25C" on the other side.

477 They are packaged in foil strips and are available in a carton of 60 (NDC 0173-0734-00)
478 tablets.

479 ZANTAC 150 EFFERdose Tablets (ranitidine HCl equivalent to 150 mg of ranitidine)
480 are white to pale yellow, round, flat-faced, bevel-edged tablets embossed with "ZANTAC
481 150" on one side and "427" on the other. They are packaged individually in foil and are
482 available in a carton of 60 (NDC 0173-0427-02) tablets.

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

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

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

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GlaxoSmithKline
Research Triangle Park, NC 27709

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