

LACHMAN CONSULTANT SERVICES, INC.
CONSULTANTS TO THE PHARMACEUTICAL AND ALLIED INDUSTRIES

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June 10, 2005

OVERNIGHT COURIER 6/10/05

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

Dear Sir or Madam:

The undersigned submits this petition, in quadruplicate, pursuant to Section 505(j)(2)(C) of the Federal Food, Drug and Cosmetic Act and in accordance with 21 CFR 10.30 on behalf of a client requesting the Commissioner of Food and Drug to declare that the drug product, Ranitidine Hydrochloride Suspension (15 mg base/mL) is suitable for consideration in an abbreviated new drug application (ANDA).

A. Action Requested

The petitioner requests that the Commissioner declare that Ranitidine Hydrochloride Suspension (15 mg base/mL) is suitable for submission as an ANDA. The reference-listed drug (RLD) product upon which this petition is based is Zantac® Tablets (Ranitidine Hydrochloride) 300 mg. Zantac® Tablets, 300 mg is approved under NDA 18-073 and is manufactured by GlaxoSmithKline. A copy of the appropriate page from the electronic Orange Book, *Approved Drug Products with Therapeutic Equivalence Evaluations*, 24th edition, that lists the approval is provided in Attachment 1. The petitioner seeks a change in the dosage form, from a tablet to a suspension of 15 mg base/mL, from that of the RLD product. The appropriate dose will be obtained by selecting the correct volume of suspension to match the tablet dose.

B. Statement of Grounds

The RLD product, Zantac® Tablets, is currently available in a 300 mg tablet dosage form, and is also approved in a 150 mg tablet strength. In addition, Zantac® is approved in an oral syrup dosage form, as well as an effervescent tablet and effervescent powder in a packet. The proposed suspension drug product will be consistent with the currently approved RLD product's labeling with the exception of the dosage form and directions for administration (because the proposed product is an oral suspension). Each mL of the proposed suspension will contain 15 mg of ranitidine base (16.8 mg ranitidine hydrochloride) and the sponsor will, in its application, provide information demonstrating that its proposed product is bioequivalent to the RLD product, Zantac® Tablets, 300 mg.

2005P-0228

The proposed product will provide an alternate dosage form that may prove to be more convenient for patients who have difficulty swallowing a tablet. The proposed product will be labeled in accordance with the approved labeling of the RLD product upon which this petition is based. Any difference in the labeling will relate solely to the difference in dosage form and the method of administration (because the proposed product is an oral suspension) and those differences that may be necessary because the products are made by different manufacturers or because of patent or exclusivity protections.

Copies of the labeling of the RLD product upon which this petition is based and draft labeling for the proposed product are included in Attachments 2 and 3, respectively. The proposed labeling is the same as the approved RLD product labeling, including the recommended doses, indications and conditions of use, with the permitted exceptions identified above.

The petitioner requests that the Commissioner find that a change in dosage form from a tablet to an oral suspension raises no questions of safety or effectiveness.

Pediatric Waiver Request

In December of 2003, Congress passed the Pediatric Research Equity Act of 2003 that amended the Federal Food, Drug, and Cosmetic Act to provide the Agency authority to require drug firms to study drugs in pediatric patients, if the Agency concludes that such study would provide beneficial health data for that patient population. The Act specifically requires that a request for a new dosage form is subject to a pediatric evaluation. The act also provides for a waiver from such requirement if the drug:

(I) does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(II) is not likely to be used in a substantial number of pediatric patients.

The petitioner hereby requests that a waiver from the conduct of pediatric studies be granted for the approval of this petition to permit an ANDA filing.

The RLD product is currently available in a conventional immediate-release tablet, an effervescent tablet and powder, as well as oral syrup. The labeling of the RLD has comprehensive instructions for pediatric use and dosing for patients down to 1 month of age. The NDA holder for Zantac received a written request for pediatric studies, conducted those studies, and received a 6-month period of pediatric exclusivity associated with those studies. Based on the submission of these studies and consistent with the rules governing pediatric exclusivity, the 6-month pediatric exclusivity extension for existing patents or exclusivity was applied to all of the innovator's products containing ranitidine hydrochloride. In that regard, because the requirements for the conduct of pediatric studies were satisfied by those studies submitted by the innovator in response to the written request, there should be no need to repeat such studies or engage in additional studies for the product proposed by this petition seeking the same condition of use as that of the RLD product upon which this petition is based. The change in dosage form to an oral suspension from an immediate-release tablet provides a more convenient dosage form for patients that do not want to or cannot take a tablet product. The proposed product also has similar functionality to other approved versions of the RLD, and thus, the proposed change in dosage form does not represent a meaningful therapeutic benefit over

existing therapies and would likely be used only for those patients for whom treatment is currently indicated in the labeling.

C. Environmental Impact

The petitioner claims a categorical exclusion under 21 CFR 25.31.

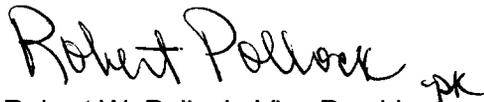
D. Economic Impact

The petitioner believes that this is not applicable in this case, but agrees to provide such an analysis if requested by the Agency.

E. Certification

The undersigned certifies that to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and includes representative data and information known to the petitioner, which are unfavorable to the petition.

Respectfully submitted,



Robert W. Pollock, Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, NY 11590

RWP/pk

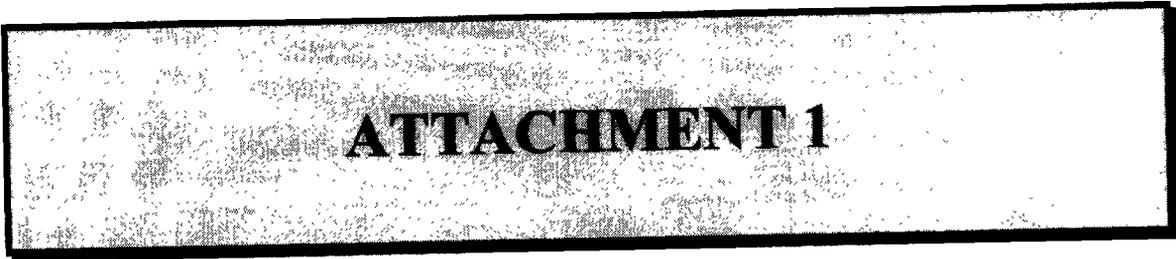
Attachments:

1. *Approved Drug Products with Therapeutic Equivalence Evaluations*, 24th edition
2. Zantac® Tablets approved labeling
3. Draft labeling for the proposed ranitidine hydrochloride oral suspension

cc: Emily Thakur (Office of Generic Drugs)

C45P5161

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590



ATTACHMENT 1

Search results from the "OB_Rx" table for query on "018703."

Active Ingredient: RANITIDINE HYDROCHLORIDE
Dosage Form;Route: TABLET; ORAL
Proprietary Name: ZANTAC 150
Applicant: GLAXOSMITHKLINE
Strength: EQ 150MG BASE
Application Number: 018703
Product Number: 001
Approval Date: Jun 9, 1983
Reference Listed Drug: No
RX/OTC/DISCN: RX
TE Code: **AB**
Patent and Exclusivity Info for this product: [View](#)

Active Ingredient: RANITIDINE HYDROCHLORIDE
Dosage Form;Route: TABLET; ORAL
Proprietary Name: ZANTAC 300
Applicant: GLAXOSMITHKLINE
Strength: EQ 300MG BASE
Application Number: 018703
Product Number: 002
Approval Date: Dec 9, 1985
Reference Listed Drug: Yes
RX/OTC/DISCN: RX
TE Code: **AB**
Patent and Exclusivity Info for this product: [View](#)

[Return to Electronic Orange Book Home Page](#)

FDA/Center for Drug Evaluation and Research

Office of Generic Drugs

Division of Labeling and Program Support

Update Frequency:

Orange Book Data - **Monthly**

Generic Drug Product Information & Patent Information - **Daily**

Orange Book Data Updated Through April, 2005

Patent and Generic Drug Product Data Last Updated: June 10, 2005

LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590



ATTACHMENT 2

PRESCRIBING INFORMATION

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

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

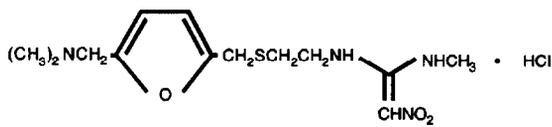
ZANTAC[®] 25
(ranitidine hydrochloride effervescent)
EFFERdose[®] Tablets

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:



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The empirical formula is C₁₃H₂₂N₄O₃S·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

35 Yellow No. 6 Aluminum Lake, hypromellose, magnesium stearate, microcrystalline cellulose,
36 titanium dioxide, triacetin, and yellow iron oxide.

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

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

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

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

57 **CLINICAL PHARMACOLOGY**

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

61 **Pharmacokinetics:**

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

69 **Distribution:** The volume of distribution is about 1.4 L/kg. Serum protein binding averages
70 15%.

71 **Metabolism:** In humans, the N-oxide is the principal metabolite in the urine; however, this
72 amounts to <4% of the dose. Other metabolites are the S-oxide (1%) and the desmethyl ranitidine
73 (1%). The remainder of the administered dose is found in the stool. Studies in patients with

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

76 **Excretion:** The principal route of excretion is the urine, with approximately 30% of the
77 orally administered dose collected in the urine as unchanged drug in 24 hours. Renal clearance is
78 about 410 mL/min, indicating active tubular excretion. The elimination half-life is 2.5 to 3 hours.
79 Four patients with clinically significant renal function impairment (creatinine clearance 25 to
80 35 mL/min) administered 50 mg of ranitidine intravenously had an average plasma half-life of
81 4.8 hours, a ranitidine clearance of 29 mL/min, and a volume of distribution of 1.76 L/kg. In
82 general, these parameters appear to be altered in proportion to creatinine clearance (see
83 DOSAGE AND ADMINISTRATION).

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

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

96

97 **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

98

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

103 **Pharmacodynamics:** Serum concentrations necessary to inhibit 50% of stimulated gastric
104 acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum

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

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

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

113

114 **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

115

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

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

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

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

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

125 **Other Pharmacologic Actions:**

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

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

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

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

133 *e.* No antiandrogenic action.

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

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

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

140

141 **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%)

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

143 [†]P<0.0001.

144

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

147

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

	Ulcer Healed	Ulcer Not Healed
ZANTAC	0.06	0.71
Placebo	0.71	1.43

149

150 Foreign studies have shown that patients heal equally well with 150 mg b.i.d. and 300 mg h.s.
 151 (85% versus 84%, respectively) during a usual 4-week course of therapy. If patients require
 152 extended therapy of 8 weeks, the healing rate may be higher for 150 mg b.i.d. as compared to
 153 300 mg h.s. (92% versus 87%, respectively).

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

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

161

162 **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

163 % = Life table estimate.

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

165 RAN = ranitidine (ZANTAC).

166 PLC = placebo.

167

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

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

174

175 **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 (12%)
Week 2				
Week 6		50/73 (68%) [†]		35/69 (51%)

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

177 [†] $P = 0.009$.

178

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

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

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

185 **Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):**
186 ZANTAC inhibits gastric acid secretion and reduces occurrence of diarrhea, anorexia, and pain
187 in patients with pathological hypersecretion associated with Zollinger-Ellison syndrome,
188 systemic mastocytosis, and other pathological hypersecretory conditions (e.g., postoperative,
189 "short-gut" syndrome, idiopathic). Use of ZANTAC was followed by healing of ulcers in 8 of 19
190 (42%) patients who were intractable to previous therapy.

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

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

201 In 2 additional US multicenter, double-blind, placebo-controlled, 2-week trials, ZANTAC
202 150 mg b.i.d. was shown to provide relief of heartburn pain within 24 hours of initiating therapy
203 and a reduction in the frequency of severity of heartburn. In these trials, ZANTAC EFFERdose
204 Tablets were shown to provide heartburn relief within 45 minutes of dosing.

205 **Erosive Esophagitis:** In 2 multicenter, double-blind, randomized, placebo-controlled,
206 12-week trials performed in the United States, ZANTAC 150 mg q.i.d. was significantly more
207 effective than placebo in healing endoscopically diagnosed erosive esophagitis and in relieving
208 associated heartburn. The erosive esophagitis healing rates were as follows:

209
210

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%) [†]

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

212 [†]P<0.001 versus placebo.

213

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

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

220 **INDICATIONS AND USAGE**

221 ZANTAC is indicated in:

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

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

245 **CONTRAINDICATIONS**

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

248 **PRECAUTIONS**

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

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

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

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

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

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

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

274 In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were
275 higher during b.i.d. dosing of ranitidine than triazolam given alone. The mean area under the
276 triazolam concentration-time curve (AUC) values in 18- to 60-year-old subjects were 10% and
277 28% higher following administration of 75-mg and 150-mg ranitidine tablets, respectively, than
278 triazolam given alone. In subjects older than 60 years of age, the mean AUC values were
279 approximately 30% higher following administration of 75-mg and 150-mg ranitidine tablets. It
280 appears that there were no changes in pharmacokinetics of triazolam and α -hydroxytriazolam, a
281 major metabolite, and in their elimination. Reduced gastric acidity due to ranitidine may have
282 resulted in an increase in the availability of triazolam. The clinical significance of this triazolam
283 and ranitidine pharmacokinetic interaction is unknown.

284 **Carcinogenesis, Mutagenesis, Impairment of Fertility:** There was no indication of
285 tumorigenic or carcinogenic effects in life-span studies in mice and rats at dosages up to
286 2,000 mg/kg per day.

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

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

291 **Pregnancy: Teratogenic Effects:** Pregnancy Category B. Reproduction studies have been
292 performed in rats and rabbits at doses up to 160 times the human dose and have revealed no
293 evidence of impaired fertility or harm to the fetus due to ZANTAC. There are, however, no

294 adequate and well-controlled studies in pregnant women. Because animal reproduction studies
295 are not always predictive of human response, this drug should be used during pregnancy only if
296 clearly needed.

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

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

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

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

310 **Geriatric Use:** Of the total number of subjects enrolled in US and foreign controlled clinical
311 trials of oral formulations of ZANTAC, for which there were subgroup analyses, 4,197 were 65
312 and over, while 899 were 75 and over. No overall differences in safety or effectiveness were
313 observed between these subjects and younger subjects, and other reported clinical experience has
314 not identified differences in responses between the elderly and younger patients, but greater
315 sensitivity of some older individuals cannot be ruled out.

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

322 **ADVERSE REACTIONS**

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

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

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

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

335 **Hepatic:** There have been occasional reports of hepatocellular, cholestatic, or mixed hepatitis,
336 with or without jaundice. In such circumstances, ranitidine should be immediately discontinued.
337 These events are usually reversible, but in rare circumstances death has occurred. Rare cases of
338 hepatic failure have also been reported. In normal volunteers, SGPT values were increased to at
339 least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for
340 7 days, and in 4 of 24 subjects receiving 50 mg q.i.d. intravenously for 5 days.

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

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

346 **Endocrine:** Controlled studies in animals and man have shown no stimulation of any pituitary
347 hormone by ZANTAC and no antiandrogenic activity, and cimetidine-induced gynecomastia and
348 impotence in hypersecretory patients have resolved when ZANTAC has been substituted.
349 However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in
350 male patients receiving ZANTAC, but the incidence did not differ from that in the general
351 population.

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

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

356 **OVERDOSAGE**

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

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

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

367 **DOSAGE AND ADMINISTRATION**

368 **Active Duodenal Ulcer:** The current recommended adult oral dosage of ZANTAC for
369 duodenal ulcer is 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of
370 ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL of syrup (4 teaspoonfuls of
371 syrup equivalent to 300 mg of ranitidine) once daily after the evening meal or at bedtime can be

372 used for patients in whom dosing convenience is important. The advantages of one treatment
373 regimen compared to the other in a particular patient population have yet to be demonstrated (see
374 Clinical Trials: *Active Duodenal Ulcer*). Smaller doses have been shown to be equally effective
375 in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that
376 100 mg twice daily is as effective as the 150-mg dose.

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

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

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

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

390 **Maintenance of Healing of Gastric Ulcers:** The current recommended adult oral dosage is
391 150 mg or 10 mL of syrup (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) at
392 bedtime.

393 **GERD:** The current recommended adult oral dosage is 150 mg or 10 mL of syrup
394 (2 teaspoonfuls of syrup equivalent to 150 mg of ranitidine) twice a day.

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

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

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

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

405 **Treatment of Duodenal and Gastric Ulcers:** The recommended oral dose for the
406 treatment of active duodenal and gastric ulcers is 2 to 4 mg/kg twice daily to a maximum of
407 300 mg/day. This recommendation is derived from adult clinical studies and pharmacokinetic
408 data in pediatric patients.

409 **Maintenance of Healing of Duodenal and Gastric Ulcers:** The recommended oral
410 dose for the maintenance of healing of duodenal and gastric ulcers is 2 to 4 mg/kg once daily to a

411 maximum of 150 mg/day. This recommendation is derived from adult clinical studies and
412 pharmacokinetic data in pediatric patients.

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

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

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

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

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

435 **HOW SUPPLIED**

436 ZANTAC 150 Tablets (ranitidine HCl equivalent to 150 mg of ranitidine) are peach,
437 film-coated, 5-sided tablets embossed with "ZANTAC 150" on one side and "Glaxo" on the
438 other. They are available in bottles of 60 (NDC 0173-0344-42), 180 (NDC 0173-0344-17), 500
439 (NDC 0173-0344-14), and 1,000 (NDC 0173-0344-12) tablets and unit dose packs of 100 (NDC
440 0173-0344-47) tablets.

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

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

447 ZANTAC 25 EFFERdose Tablets (ranitidine HCl equivalent to 25 mg of ranitidine) are white
448 to pale yellow, round, flat-faced, bevel-edged tablets embossed with "GS" on one side and

449 "25C" on the other side. They are packaged in foil strips and are available in a carton of 60
450 (NDC 0173-0734-00) tablets.

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

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

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

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

461
462



463
464 GlaxoSmithKline
465 Research Triangle Park, NC 27709

466
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468 license.

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471
472 October 2004

RL-2131

Zantac 25
EFFERdose Tablets
(ranitidine hydrochloride effervescent)
25 mg

Zantac 25
EFFERdose Tablets
(ranitidine hydrochloride effervescent)
25 mg

Zantac 25
EFFERdose Tablets
(ranitidine hydrochloride effervescent)
25 mg

Pharmaceuticals: Contains phenylephrine 2.5 mg per 25 mg
Do not swallow tablet. Dissolve before use.

See prescribing information for dosage information.
Store between 2° and 30°C (36° and 86°F).

Zantac and EFFERdose are registered trademarks of
Warner-Lambert Company, used under license.

GlaxoSmithKline
GlaxoSmithKline
Research Triangle Park, NC 27709
Made in France

LOT & EXP



AD10116

Zantac 25
EFFERdose Tablets
(ranitidine hydrochloride effervescent)
25 mg

Zantac 25
EFFERdose Tablets
(ranitidine hydrochloride effervescent)
25 mg

Zantac 25
EFFERdose Tablets
(ranitidine hydrochloride effervescent)
25 mg

GlaxoSmithKline

GlaxoSmithKline

AD10116
Rev. 10/04

Zantac 25

(Lambert Nutrition Inc. - Effendose)
EFFERdose tablets

25 mg

Pharmaceuticals, Inc. is a subsidiary of
Pfizer Inc.

For more information, please contact
Lambert Nutrition Inc., 1000
Lambert Blvd., St. Louis, MO 63103
or call 1-800-368-2277.

Zantac 25

(Lambert Nutrition Inc. - Effendose)
EFFERdose tablets
25 mg



Zantac 25

(Lambert Nutrition Inc. - Effendose)
EFFERdose tablets

25 mg

Pharmaceuticals, Inc. is a subsidiary of
Pfizer Inc.

Sample - Not for Sale

Zantac 25

(Lambert Nutrition Inc. - Effendose)
EFFERdose tablets
25 mg

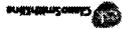
(Lambert Nutrition Inc. - Effendose)
EFFERdose tablets
25 mg

1164804

1164804
11/03
Rev 11/03



For Inside Flip Top Foil Packet Instructions
See Inside Flip Top Foil Packet Instructions



Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

P20117A
P20117A
P20117A
P20117A

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

Phenylethanolamine: Contains phenylethanolamine 2.81 mg per 25 mg
Do not swallow tablet. Dissolve before use.
See prescribing information for dosage information.
Store between 2° and 30°C (36° and 86° F).
Do not use if foil packet is torn or broken.

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

LOT & EXP



Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

Rx only



Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

Tablet is not to be chewed, swallowed whole,
or dissolved on the tongue.



ZEF001

ZEF001
Rev. 10/04



Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose® Tablets 25 mg

PREPARATION INSTRUCTIONS

It is important to follow these 3 steps in order to take Zantac 25.



1. Drop 1 tablet in to the
glass and immediately
fill with water.



2. Stir tablet to completely
dissolve before use.



3. Solution may be given
with medicine dropper or
small spoon.

Tablet is not to be chewed, swallowed whole, or dissolved on the tongue.

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

Phenylketonurics: Contains phenylalanine 2.81 mg per 25 mg

Do not swallow tablet. Dissolve before use.

See prescribing information for dosage information.

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

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

NDC 0173-0734-00



Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets

Rx only

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg



N 0173-0734-00 6

GlaxoSmithKline
Research Triangle Park, NC 27709
Made in France

4153812

4153812
Rev. 12/03

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets 25 mg

PREPARATION INSTRUCTIONS
Please refer to the following instructions for use.

-  1. Drop 1 tablet in no less than one teaspoonful (5 mL) of water.
-  2. Allow tablet to completely dissolve before use.
-  3. Solution may be given with medicine dropper or oral syringe.

Tablet is not to be chewed, swallowed whole, or dissolved on the tongue.

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets 25 mg

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose Tablets 25 mg

See prescribing information for dosage information.
Store between 2° and 30°C (36° and 86°F).
Do not use if foil packet is torn or broken.
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LOT & EXP

AD10117

AD10117 Rev. 10/04

Do not swallow tablet.
Dissolve before use.

Pharmaceutical
Contains phenylephrine
2.51 mg per 25 mg

Zantac 25
EFFERdose Tablets

Zantac 25

(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

Zantac 25

(ranitidine hydrochloride effervescent)
EFFERdose Tablets
25 mg

**Phenylketonurics: Contains phenylalanine 2.81 mg
per 25 mg.
Do not swallow tablet. Dissolve before use.**



Sample—Not for Sale

2 Tablets

Zantac 25
(ranitidine hydrochloride effervescent)
EFFERdose[®] Tablets
25 mg

Do not swallow tablet. Dissolve before use.

Dissolve one tablet in no less than 1 teaspoonful (5 mL) of water in an appropriate measuring cup before use.

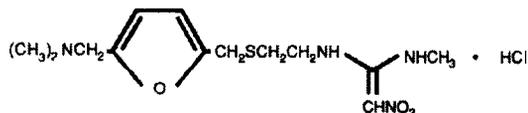
LACHMAN CONSULTANT SERVICES, INC.
Westbury, NY 11590

ATTACHMENT 3

Ranitidine Hydrochloride Suspension

DESCRIPTION

The active ingredient in RANITIDINE HYDROCHLORIDE Suspension 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 C₁₃H₂₂N₄O₃S•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 sulfur-like odor.

Each 1 mL of RANITIDINE HYDROCHLORIDE Suspension contains 16.8 mg of ranitidine HCl equivalent to 15 mg of ranitidine. *Inactive ingredient information will be supplied when the ANDA is submitted.*

CLINICAL PHARMACOLOGY

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

Pharmacokinetics:

Absorption: RANITIDINE HYDROCHLORIDE 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. Absorption is not significantly impaired by the administration of food or antacids. Propantheline slightly delays and increases peak blood levels of RANITIDINE HYDROCHLORIDE, 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 RANITIDINE HYDROCHLORIDE.

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 ($t_{1/2}$, V_d , 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	1 to 2 mg/kg	54 to 492	2.0
Otherwise healthy requiring RANITIDINE HYDROCHLORIDE (0.7 to 14 years, Single dose)	10	2 mg/kg	244	1.61
Otherwise healthy requiring RANITIDINE HYDROCHLORIDE (0.7 to 14 years, Multiple dose)	10	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 RANITIDINE HYDROCHLORIDE are in this range up to 12 hours. However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

Antisecretory Activity: 1. Effects on Acid Secretion: RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE, 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 RANITIDINE HYDROCHLORIDE does not affect pepsin secretion. Total pepsin output is reduced in proportion to the decrease in volume of gastric juice.

Intrinsic Factor: Oral RANITIDINE HYDROCHLORIDE has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: RANITIDINE HYDROCHLORIDE 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 (IV) 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: 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 RANITIDINE HYDROCHLORIDE as shown in Table 3.

Table 3. Duodenal Ulcer Patient Healing Rates

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

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

In these studies, patients treated with RANITIDINE HYDROCHLORIDE 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
RANITIDINE HYDROCHLORIDE	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 RANITIDINE HYDROCHLORIDE (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.

* = $P < 0.05$ (RANITIDINE HYDROCHLORIDE versus comparator).

RAN = ranitidine (RANITIDINE HYDROCHLORIDE).

PLC = placebo.

As with other H₂-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 RANITIDINE HYDROCHLORIDE as shown in Table 6.

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 (12%)
Week 2				50/73 (68%)†
Week 6				

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

. $P = 0.009$.

In this multicenter trial, significantly more patients treated with RANITIDINE HYDROCHLORIDE 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, RANITIDINE HYDROCHLORIDE 150 mg h.s. was significantly more effective than placebo in maintaining healing of gastric ulcers.

Pathological Hypersecretory Conditions (such as Zollinger-Ellison syndrome):

RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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, RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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, RANITIDINE HYDROCHLORIDE 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.

Erosive Esophagitis: In 2 multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, RANITIDINE HYDROCHLORIDE 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	RANITIDINE HYDROCHLORIDE 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, RANITIDINE HYDROCHLORIDE 150 mg b.i.d. was significantly more effective than placebo in maintaining healing of erosive esophagitis.

INDICATIONS AND USAGE

RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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

RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE does not preclude the presence of gastric malignancy.

2. Since RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE is metabolized in the liver.

3. Rare reports suggest that RANITIDINE HYDROCHLORIDE may precipitate acute porphyric attacks in patients with acute porphyria. RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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, 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. 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 RANITIDINE HYDROCHLORIDE. There are, however, no 10 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: RANITIDINE HYDROCHLORIDE is secreted in human milk. Caution should be exercised when RANITIDINE HYDROCHLORIDE is administered to a nursing mother.

Pediatric Use: The safety and effectiveness of RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE 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 RANITIDINE HYDROCHLORIDE, 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 RANITIDINE HYDROCHLORIDE. The relationship to therapy with RANITIDINE HYDROCHLORIDE has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of RANITIDINE HYDROCHLORIDE.

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 H₂-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 RANITIDINE HYDROCHLORIDE and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when RANITIDINE HYDROCHLORIDE has been substituted.

However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving RANITIDINE HYDROCHLORIDE, 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 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 RANITIDINE HYDROCHLORIDE 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 LD₅₀ 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 RANITIDINE HYDROCHLORIDE for duodenal ulcer is 150 mg or 10 mL of Suspension (2 teaspoonfuls of Suspension equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL of Suspension (4 teaspoonfuls of Suspension 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 Suspension (2 teaspoonfuls of Suspension 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 Suspension (2 teaspoonfuls of Suspension equivalent to 150 mg of ranitidine) twice a day. In some patients it may be necessary to administer RANITIDINE HYDROCHLORIDE 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 Suspension (2 teaspoonfuls of Suspension 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 Suspension (2 teaspoonfuls of Suspension equivalent to 150 mg of ranitidine) at bedtime.

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

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

Pediatric Use: The safety and effectiveness of RANITIDINE HYDROCHLORIDE have been established in the age-group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of RANITIDINE HYDROCHLORIDE 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

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 RANITIDINE

HYDROCHLORIDE, the recommended dosage in patients with a creatinine clearance <50 mL/min is 150 mg or 10 mL of Suspension (2 teaspoonfuls of Suspension 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).

HOW SUPPLIED

RANITIDINE HYDROCHLORIDE Suspension 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).

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