

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	Tablets (1 to 2 mg/kg)	54 to 492	2.0
Otherwise healthy requiring Ranitidine (0.7 to 14 years, Single dose)	10	Syrup (2 mg/kg)	244	1.61
Otherwise healthy requiring Ranitidine (0.7 to 14 years, Multiple dose)	10	Syrup (2 mg/kg)	320	1.66

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

Pharmacodynamics: Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 36 to 94 ng/mL. Following a single oral dose of 150 mg, serum concentrations of Ranitidine Tablets, USP 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 Tablets, USP 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 Tablets, USP on Gastric Acid Secretion

Time After Dose, h	% Inhibition of Gastric Acid Output by Dose, mg	% Inhibition of Gastric Acid Output by Dose, mg	% Inhibition of Gastric Acid Output by Dose, mg	% 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 Tablets, USP, responding almost completely to doses of 100 mg or less, while pentagastrin- and food-stimulated secretions are most difficult to suppress.

2. Effects on Other Gastrointestinal Secretions:

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

Intrinsic Factor: Oral Ranitidine Tablets, USP has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Serum Gastrin: Ranitidine Tablets, USP 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 two or three 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 Tablets, USP as shown in Table 3

Table 3. Duodenal Ulcer Patient Healing Rates

	Ranitidine	Ranitidine	placebo*	placebo*
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	Tablets, USP *	Tablets, USP *	Placebo**	Placebo**
	Number Entered	Healed/Evaluable	Number Entered	Healed/Evaluable
Outpatients				
Week 2	195	69/182 (38%) †	188	31/164(19%)
Week 4	195	76/168 (45%)	188	76/168(45%)

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

†P less than 0.0001.

In these studies, patients treated with Ranitidine Tablets, USP 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 Tablets, USP	0.06	0.71
Placebo	0.71	1.43

oreign 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 Tablets, USP (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	Double-Blind, Multicenter, Placebo-Controlled Trials	Double-Blind, Multicenter, Placebo-Controlled Trials	Double-Blind, Multicenter, Placebo-Controlled Trials	Double-Blind, Multicenter, Placebo-Controlled Trials	Double-Blind, Multicenter, Placebo-Controlled Trials
Multicenter Trial	dRUG	Duodenal Ulcer Prevalence	Duodenal Ulcer Prevalence	Duodenal Ulcer Prevalence	No. Of Patients
		0-4 Months	0-8 Months	0-12 Months	
USA	RAN	20%*	24%*	35%*	138

USA	PLC	44%	54%	59%	139
Foreign	RAN	12%*	21%*	18%*	174
Foreign	PLC	56%	64%	68%	165

% = Life table estimate.

* = P less than 0.05 (Ranitidine Tablets, USP versus comparator).

RAN = ranitidine (Ranitidine Tablets, USP)

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 Tablets, USP as shown in Table 6.

Table 6. Gastric Ulcer Patient Healing Rates

	Ranitidine Tablets, USP *	Ranitidine Tablets, USP *	Placebo* 3	Placebo* 3
	Number Entered	Healed / Evaluable	Number Entered	Healed / Evaluable
Outpatients				
Week 2	92	16/183 (19%) †	94	10/83 (12%)
Week 6	92	50/73 (68%) †	94	35/69 (51%)

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

†P = 0.009.

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

Maintenance of Healing of Gastric Ulcers: In two multicenter, double-blind, randomized, placebo-controlled, 12-month trials conducted in patients whose gastric ulcers had been previously healed, Ranitidine Tablets, USP 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 Tablets, USP 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 Tablets, USP 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 Tablets, USP 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 Tablets, USP 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 Tablets, USP 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 two multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, Ranitidine Tablets, USP 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	Healed / Evaluable
	Placebo* n=229	Ranitidine Tablets, USP 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 less than 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 Tablets, USP 150 mg b.i.d. was significantly more effective than placebo in maintaining healing of erosive esophagitis

INDICATIONS AND USAGE

Ranitidine Tablets, USP 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 Tablets, USP 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 Tablets, USP 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 Tablets, USP 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 Tablets, USP does not preclude the presence of gastric malignancy.
2. Since Ranitidine Tablets, USP 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 Tablets, USP is metabolized in the liver.
3. Rare reports suggest that Ranitidine Tablets, USP may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine Tablets, USP 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 Tablets, USP therapy, and therefore testing with sulfosalicylic acid is recommended.

Drug Interactions: Although Ranitidine Tablets, USP 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 Tablets, USP may affect the bioavailability of certain drugs by some mechanism as yet unidentified (e.g., a pH-dependent effect on absorption or a change in volume of distribution).

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

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

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

Ranitidine was not mutagenic in standard bacterial tests (*Salmonella*, *Escherichia coli*) for mutagenicity at concentrations up to the maximum recommended for these assays. In a dominant lethal assay, a single oral dose of 1,000 mg/kg to male rats was without effect on the outcome of 2 matings per week for the next 9 weeks.

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

Nursing Mothers: Ranitidine Tablets, USP is secreted in human milk. Caution should be exercised when Ranitidine Tablets, USP is administered to a nursing mother.

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

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 (leucopenia, 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 Tablets, USP and no antiandrogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Ranitidine Tablets, USP has been substituted. However, occasional cases of gynecomastia, impotence, and loss of libido have been reported in male patients receiving Ranitidine Tablets, USP, but the incidence did not differ from that in the general population.

Rare cases of breast symptoms and conditions, including galactorrhea and gynecomastia, have been reported in both males and females.

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

Respiratory: A large epidemiological study suggested an increased risk of developing pneumonia in current users of histamine-2-receptor antagonists (H2RAs) compared to patients who had stopped H2RA treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07 - 2.48). However, a causal relationship between use of H2RAs and pneumonia has not been established.

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

OVERDOSAGE

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

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

Studies in dogs receiving dosages of Ranitidine Tablets, USP 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 dosage of Ranitidine Tablets, USP for duodenal ulcer is 150 mg twice daily. An alternative dosage of 300 mg 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 at bedtime.

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

The current recommended adult oral dosage is 150 mg twice a day. In some patients it may be necessary to administer Ranitidine Tablets, USP 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 twice a day.

Maintenance of Healing of Gastric Ulcers: The current recommended adult oral dosage is 150 mg at bedtime.

GERD: The current recommended adult oral dosage is 150 mg twice a day.

Erosive Esophagitis: The current recommended adult oral dosage is 150 mg four times a day.

Maintenance of Healing of Erosive Esophagitis: The current recommended adult oral dosage is 150 mg twice a day.

Pediatric Use: The safety and effectiveness of Ranitidine Tablets, USP have been established in the age-group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of Ranitidine Tablets, USP 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 two 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 Tablets, USP, the recommended dosage in patients with a creatinine clearance less than 50 mL/min is 150 mg 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 Tablets, USP 150 mg are orange, round, biconvex aqueous film coated tablets debossed "IP 253" on one side and plain on the reverse.

They are available in bottles of 24, 60, 100, 180, 500 and 1000.

Ranitidine Tablets, USP 300 mg are yellow, capsule-shaped aqueous film coated tablets debossed "IP 254" on one side and plain on the reverse.

They are available in bottles of 24, 30, 100, 250, 500 and 1000.

Manufactured by:
Amneal Pharmaceuticals of NY
Hauppauge, NY 11788

Distributed by:
Amneal Pharmaceuticals
Glasgow, KY 42141

Rev. 11-2009

Store at 20° - 25°C (68° - 77°F) (See USP Controlled Room Temperature) in a tight, light resistant container. Protect from light. Replace cap securely after each opening.

NDC 53476-253-05 Ranitidine Tablets, USP IP253 150 mg Rx only 500 TABLETS amneal PHARMACEUTICALS Each tablet contains: 150 mg of ranitidine as ranitidine hydrochloride. See package insert for Dosage and Administration. Store at 20 degree - 25 degree Centigrade (68 degree - 77 degree F) (See USP Controlled Room Temperature) in a tight, light resistant container. Protect from light. Replace cap securely after each opening. Manufactured by: Amneal Pharmaceuticals of NY Hauppauge, NY 11788 Distributed by: Amneal Pharmaceuticals Glasgow, KY 42141 MF# 107 Rev. 07-2008 N3 53746 - 253 - 05 7 Lot No: Exp. Date:

GABAdone (US patent pending) capsules by oral administration. A specially formulated Medical Food product, consisting of a proprietary blend of amino acids and polyphenol ingredients in specific proportions, for the dietary management of the metabolic processes of sleep disorders (SD). Must be administered under physician supervision.

Medical Foods

Medical Food products are often used in hospitals (e.g., for burn victims or kidney dialysis patients) and outside of a hospital setting under a physician's care for the dietary management of diseases in patients with particular medical or metabolic needs due to their disease or condition. Congress defined "Medical Food" in the Orphan Drug Act and Amendments of 1988 as "a system which is formulated to be consumed or administered enterally [or orally] under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." Medical Foods are complex formulated products, requiring sophisticated and exacting technology. GABAdone has been developed, manufactured, and labeled in accordance with both the statutory and the FDA regulatory definition of a Medical Food. GABAdone must be used while the patient is under the ongoing care of a physician.

SLEEP DISORDERS (SD)

SD as a Metabolic Deficiency Disease

A critical component of the definition of a Medical Food is the requirement for a distinctive nutritional deficiency. FDA scientists have proposed a physiologic definition of a distinctive nutritional deficiency as follows: "the dietary management of patients with specific diseases requires, in some instances, the ability to meet nutritional requirements that differ substantially from the needs of healthy persons. For example, in establishing the recommended dietary allowances for general, healthy population, the Food and Nutrition Board of the Institute of Medicine National Academy of Sciences, recognized that different or distinctive physiologic requirements may exist for certain persons with "special nutritional needs arising from metabolic disorders, chronic diseases, injuries, premature birth, other medical conditions and drug therapies. Thus, the distinctive nutritional needs associated with a disease reflect the total amount needed by a healthy person to support life or maintain homeostasis, adjusted for the distinctive changes in the nutritional needs of the patient as a result of the effects of the disease process on absorption, metabolism, and excretion." It was also proposed that in patients with certain disease states who respond to nutritional therapies, a physiologic deficiency of the nutrient is assumed to exist. For example, if a patient with sleep disorders responds to a tryptophan formulation by improving the duration and quality of sleep, a deficiency of tryptophan is assumed to exist.

Patients with sleep disorders are known to have nutritional deficiencies of tryptophan, choline, flavonoids, and certain antioxidants. Patients with sleep disorders frequently exhibit reduced plasma levels of tryptophan and have been shown to respond to oral administration of tryptophan or a 5-hydroxytryptophan formulation. Research has shown that tryptophan reduced diets result in a fall in circulating tryptophan. Patients with sleep disorders frequently experience activation of the tryptophan degradation pathway that increases the turnover of tryptophan leading to a reduced level of production of serotonin for a given tryptophan blood level. Research has also shown that a genetic predisposition to accelerated tryptophan degradation can lead to increased tryptophan requirements in certain patients with sleep disorders.

Choline is required to fully potentiate acetylcholine synthesis by brain neurons. A deficiency of choline leads to reduced acetylcholine production by the neurons. Low fat diets, frequently used by patients with sleep disorders, are usually choline deficient. Flavonoids potentiate the production of acetylcholine by the neurons thereby inducing REM sleep. Low fat diets and diets deficient in flavonoid rich foods result in inadequate flavonoid concentrations, impeding acetylcholine production in certain patients with sleep disorders. Provision of tryptophan, choline, and flavonoids with antioxidants, in specific proportions can restore the production of beneficial serotonin and acetylcholine, thereby improving sleep quality.

PRODUCT DESCRIPTION

Primary Ingredients

GABAdone consists of a proprietary blend of amino acids, cocoa, ginkgo biloba and flavonoids in specific proportions. These ingredients fall into the category of “Generally Regarded as Safe” (GRAS) as defined by the Food and Drug Administration (FDA) (Sections 201(s) and 409 of the Federal Food, Drug, and Cosmetic Act). A GRAS substance is distinguished from a food additive on the basis of the common knowledge about the safety of the substance for its intended use. The standard for an ingredient to achieve GRAS status requires not only technical demonstration of non-toxicity and safety, but also general recognition of safety through widespread usage and agreement of that safety by experts in the field. Many ingredients have been determined by the U.S. Food and Drug Administration (FDA) to be GRAS, and are listed as such by regulation, in Volume 21 Code of Federal Regulations (CFR) Sections 182, 184, and 186.

Amino Acids

Amino Acids are the building blocks of protein. All amino acids are GRAS listed as they have been ingested by humans for thousands of years. The doses of the amino acids in GABAdone are equivalent to those found in the usual human diet; however the formulation uses specific ratios of the key ingredients to elicit a therapeutic response. Tryptophan, for example, is an obligatory amino acid. The body cannot make tryptophan and must obtain tryptophan from the diet. Tryptophan is needed to produce serotonin. Serotonin is required to induce sleep. Patients with sleep disorders have altered serotonin metabolism. Some patients with sleep disorders have a resistance to the use of tryptophan that is similar to the mechanism found in insulin resistance. Patients with sleep disorders cannot acquire sufficient tryptophan from the diet to establish normal sleep architecture without ingesting a prohibitively large amount of calories, particularly calories from protein.

Flavonoids

Flavonoids are a group of phytochemical compounds found in all vascular plants including fruits and vegetables. They are a part of a larger class of compounds known as polyphenols. Many of the therapeutic or health benefits of colored fruits and vegetables, cocoa, red wine, and green tea are directly related to their flavonoid content. The amounts of specially formulated flavonoids found in GABAdone cannot be obtained from conventional foods in the necessary proportions to elicit a therapeutic response.

Physical Description

GABAdone is a yellow to light brown powder. GABAdone contains L-Glutamic Acid, 5-Hydroxytryptophan as Griffonia Seed Extract, Acetyl L-Carnitine HCL, Gamma Amino Butyric Acid, Choline Bitartrate, Hydrolyzed Whey Protein, Cocoa, Ginkgo Biloba, Valerian Root, and Grape Seed Extract.

Other Ingredients

GABAdone contains the following inactive or other ingredients, as fillers, excipients, and colorings: magnesium stearate, microcrystalline cellulose, Maltodextrin NF, gelatin (as the capsule material).

CLINICAL PHARMACOLOGY

Mechanism of Action

GABAdone acts by restoring and maintaining the balance of the neurotransmitters, serotonin, and acetylcholine that are required for maintaining normal sleep architecture. A deficiency of these neurotransmitters is associated with sleep disorders.

Metabolism

The amino acids in GABAdone are primarily absorbed by the stomach and small intestines. All cells metabolize the amino acids in GABAdone. Circulating tryptophan and choline blood levels determine the production of serotonin and acetylcholine.

Excretion

GABAdone is not an inhibitor of cytochrome P450 1A2, 2C9, 2C19, 2D6, or 3A4. These isoenzymes are principally responsible for 95% of all detoxification of drugs, with CYP3A4 being responsible for detoxification of roughly 50% of drugs. Amino acids do not appear to have an effect on drug metabolizing enzymes.

INDICATIONS FOR USE

GABAdone is intended for the clinical dietary management of the metabolic processes in patients with sleep disorders and sleep disorders associated with anxiety.

- Insomnia
- Sleep maintenance insomnia
- Sleep disorders of circadian origin
- Sleep disorders associated with anxiety
- Snoring

CLINICAL EXPERIENCE

Patients taking GABAdone have demonstrated significant functional improvements when this therapeutic agent is used for the dietary management of the metabolic processes associated with sleep disorders. The administration of GABAdone results in the induction and maintenance of sleep in patients with sleep disorders. GABAdone has no effect on normal blood pressure.

PRECAUTIONS AND CONTRAINDICATIONS

GABAdone is contraindicated in an extremely small number of patients with hypersensitivity to any of the nutritional components of GABAdone.

ADVERSE REACTIONS

Oral supplementation with L-tryptophan or choline at high doses up to 15 grams daily is generally well tolerated. The most common adverse reactions of higher doses — from 15 to 30 grams daily — are nausea, abdominal cramps, and diarrhea. Some patients may experience these symptoms at lower doses. The total combined amount of amino acids in each GABAdone capsule does not exceed 400 mg.

DRUG INTERACTIONS

GABAdone does not directly influence the pharmacokinetics of prescription drugs. Clinical experience

has shown that administration of GABAdone may allow for lowering the dose of co-administered drugs under physician supervision.

OVERDOSE

There is a negligible risk of overdose with GABAdone as the total dosage of amino acids in a one month supply (60 capsules) is less than 25 grams. Overdose symptoms may include diarrhea, weakness, and nausea.

POST-MARKETING SURVEILLANCE

Post-marketing surveillance has shown no serious adverse reactions. Reported cases of mild rash and itching may have been associated with allergies to GABAdone flavonoid ingredients, including cinnamon, cocoa, and chocolate. The reactions were transient in nature and subsided within 24 hours.

DOSAGE AND ADMINISTRATION

Recommended Administration

For the dietary management of the metabolic processes in patients with sleep disorders. Take (2) capsules daily at bedtime. An additional dose of one or two capsules may be taken after awakenings during the night. As with most amino acid formulations GABAdone should be taken without food to increase the absorption of key ingredients.

How Supplied

GABAdone is supplied in blue and white, size 0 capsules in bottles of 60 capsules.

Physician Supervision

GABAdone is a Medical Food product available by prescription only and must be used while the patient is under ongoing physician supervision.

U.S. patent pending.

Manufactured by Arizona Nutritional Supplements, Inc. Chandler AZ 85225

Distributed by Physician Therapeutics LLC, Los Angeles, CA 90077. www.ptlcentral.com

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NDC # 68405-1004-02

Storage

Store at room temperature, 59-86OF (15-30OC) Protect from light and moisture. GABAdone is supplied to physicians in a recyclable plastic bottle with a child-resistant cap.

Directions for use: Must be administered under physician supervision. For adults only. As a Medical Food, take one (1) or two (2) capsules daily at bedtime or as directed by physician. For the dietary management of sleep disorders. Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor. Storage: Keep tightly closed in a cool dry place 8-32 degree centigrade (45-90 degree F), relative humidity, below 50%. Warning: Keep this product out of the reach of children. NDC# 68405-1004-02 PHYSICIAN THERAPEUTICS GABADONE Medical Food Rx only 60 Capsules

Ingredients: Each serving (per 2 capsules) contains: Proprietary Amino Acid Blend Choline Bitartrate, Gamma Amino Butyric Acid (GABA), Glutamic Acid (L-Glutamic Acid), Whey Protein Hydrolysate 80%, Griffonia Seed Extract (5-HTP), Cocoa Extract (fruit), Proprietary Herbal Blend Indian Valerian Extract 4:1 (root), Ginkgo Biloba (leaves), Acetyl L-Carnitine HCl, Grape Extract (95% Polyphenols) (seed) Other Ingredients L Gelatin, tricalcium phosphate, silicon dioxide, vegetable magnesium stearate, FDandC blue #1, titanium dioxide. Distributed exclusively by: Physicians Therapeutics LLC A Divisions of Targeted Medical Pharma, Inc. Los Angeles, CA 90077 www.ptlcentral.com Patent Pending 68405-1004-02

A Convenience Packed Medical Food and Drug Gabitidine PHYSICIAN THERAPEUTICS
 GABADone 60 Capsules Ranitidine 150mg 30 Tablets No Refills Without Physician Authorization
 Rx Only NDC# 68405-8004-26 of this co-pack For the Dietary Management of Sleep Disorders.
 Two capsules at bedtime or as directed by physician. See product label and insert. Gabadone Medical
 Food As prescribed by physician. See product label and product information insert. Ranitidine 150mg
 Rx Drug



68405-1004-02

Directions for use:
Must be administered under physician supervision.
 For adults only. As a Medical Food, take one (1) or two (2) capsules daily at bedtime or as directed by physician.

For the dietary management of sleep disorders.
 Contains no added sugar, starch, wheat, yeast, preservatives, artificial flavor.

Storage:
 Keep tightly closed in a cool dry place 8-32°C (45-90°F), relative humidity, below 50%.

Warning: Keep this product out of the reach of children.

NDC# 68405-1004-02



GABADONE
 Medical Food

Rx only

60 Capsules

Ingredients:
 Each serving (per 2 capsules) contains:
 Proprietary Amino Acid Blend
 Choline Bitartrate, Gamma Amino Butyric Acid (GABA), Glutamic Acid (L-Glutamic Acid), Whey Protein Hydrolysate 80%, Griffonia Seed Extract (5-HTP),
 Cocoa Extract (fruit),
 Proprietary Herbal Blend
 Indian Valerian Extract 4:1 (root),
 Ginkgo Biloba (leaves),
 Acetyl L-Carnitine HCl,
 Grape Extract (95% Polyphenols) (seed)
Other Ingredients: Gelatin, tricalcium phosphate, silicon dioxide, vegetable magnesium stearate, FD&C blue #1, titanium dioxide.
Distributed exclusively by:
Physicians Therapeutics LLC
 A Division of Targeted Medical Pharma, Inc.
 Los Angeles, CA 90077
 www.ptcentral.com
 Patent Pending

52959-0502-30

CAUTION: Federal law PROHIBITS the transfer of this drug to anyone other than the person to whom prescribed and prohibits dispensing without a prescription unless OTC. See insert for additional info. KEEP OUT OF REACH OF CHILDREN. Store in a cool dry place at 68 to 77 degrees F.

RANITIDINE 150mg TABLET



Lot #: RAN102QY

#30

Mfg: AMNEALPHRM
 Exp: 08/11

Compare to: Zantac
 Mfg. NDC: 53746-0253-05

Take as directed by your Doctor or
 See insert for usual dosage information

RANITIDINE 150mg TABLET			
52959-0502-30	Qty	#30	
08/11	Lot	RAN102QY	
Zantac		53746-0253-05	

RANITIDINE 150mg TABLET			
52959-0502-30	Qty	#30	
08/11	Lot	RAN102QY	
Zantac		53746-0253-05	

RANITIDINE 150mg TABLET			
52959-0502-30	Qty	#30	
08/11	Lot	RAN102QY	
Zantac		53746-0253-05	

RANITIDINE 150mg TABLET			
52959-0502-30	Qty	#30	
08/11	Lot	RAN102QY	
Zantac		53746-0253-05	

Repack: HJ Harris Co., Inc. Norco, CA 92441

A Convenience Packed Medical Food & Drug

GabritidineTM



- ▶ **GABAdoneTM 60 Capsules**
- ▶ **Ranitidine 150 mg 30 Tablets**

No Refills Without
Physician Authorization

Rx Only
NDC# 68405-004-26
of this co-pack

GABITIDINE

ranitidine hydrochloride, choline kit

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:68405-004
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Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:68405-004-26	1 in 1 KIT		

Quantity of Parts

Part #	Package Quantity	Total Product Quantity
Part 1	1 BOTTLE	30
Part 2	1 BOTTLE	60

Part 1 of 2

RANITIDINE

ranitidine hydrochloride tablet

Product Information

Item Code (Source)	NDC:52959-502(NDC:53746-253)
Route of Administration	ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
RANITIDINE HYDROCHLORIDE (UNII: BK76465IHM) (RANITIDINE - UNII:884KT10YB7)	RANITIDINE HYDROCHLORIDE	150 mg

Product Characteristics

Color	orange (ORANGE)	Score	no score
Shape	ROUND (Biconvex)	Size	9mm
Flavor		Imprint Code	IP253
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:52959-502-30	30 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
ANDA	ANDA077824	07/07/2011	

Part 2 of 2

GABADONE

choline capsule

Product Information

Route of Administration ORAL

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
CHOLINE (UNII: N91BDP6H0X) (CHOLINE - UNII:N91BDP6H0X)	CHOLINE	125 mg

Inactive Ingredients

Ingredient Name	Strength
MAGNESIUM STEARATE (UNII: 70097M6I30)	
CELLULOSE, MICROCRYSTALLINE (UNII: OP1R32D61U)	
MALTODEXTRIN (UNII: 7CVR7L4A2D)	
GELATIN (UNII: 2G86QN327L)	

Product Characteristics

Color	blue (BLUE WHITE)	Score	no score
Shape	CAPSULE	Size	21mm
Flavor		Imprint Code	;
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1		60 in 1 BOTTLE		

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
Medical Food		07/07/2011	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
unapproved drug other		07/07/2011	

Labeler - Physician Therapeutics LLC (931940964)

Establishment

Name	Address	ID/FEI	Business Operations
Amneal Pharmaceuticals		831227801	manufacture

Establishment

Name	Address	ID/FEI	Business Operations
H.J. Harkins Company, Inc		147681894	repack

Establishment

Name	Address	ID/FEI	Business Operations
Targeted Medical Pharma Inc.		126962740	manufacture

Revised: 8/2011

Physician Therapeutics LLC