For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

℞ Ranitidine Tablets IP 150 mg / 300 mg

RANTAC® 150 / 300

COMPOSITION

Rantac 150
Each film coated tablets contains:
Ranitidine Hydrochloride IP
Equivalent to Ranitidine …… 150 mg
Colours: Sunset Yellow FCF, Red Oxide of Iron & Titanium Dioxide IP

Rantac 300
Each film coated tablets contains:
Ranitidine Hydrochloride IP
Equivalent to Ranitidine …… 300 mg
Colours: Sunset Yellow FCF, Red Oxide of Iron & Titanium Dioxide IP

DOSAGE FORM
Film coated tablets

INDICATIONS
Ranitidine Tablets 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 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 twice daily.
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 4 times daily.
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.

DOSAGE AND METHOD OF ADMINISTRATION
Active Duodenal Ulcer: The current recommended adult oral dosage of Ranitidine Tablets 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 with the other in a particular patient population have yet to be demonstrated. 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.
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 daily. Dosages should be adjusted to individual patient needs, and should continue as long as clinically indicated.
Benign Gastric Ulcer: The current recommended adult oral dosage is 150 mg twice daily.
Maintenance of Healing of Gastric Ulcers: The current recommended adult oral dosage is 150 mg at bed time.
GERD: The current recommended adult oral dosage is 150 mg twice daily.
Erosive Esophagitis: The current recommended adult oral dosage is 150 mg 4 times daily.
Maintenance of Healing of Erosive Esophagitis: The current recommended adult oral dosage is 150 mg twice daily.
Pediatric Use: The safety and effectiveness of Ranitidine Tablets have been established in the age- group of 1 month to 16 years. There is insufficient information about the pharmacokinetics of Ranitidine Tablets 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 to 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/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 Tablets, the recommended dosage in patients with a creatinine clearance < 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.

CONTRAINDICATIONS
Ranitidine Tablets is contraindicated for patients known to have hypersensitivity to the drug or any of the ingredients (see WARNINGS AND PRECAUTIONS).

WARNING AND PRECAUTIONS
General:
1. Symptomatic response to therapy with Ranitidine Tablets does not preclude the presence of gastric malignancy.
2. Since Ranitidine Tablets is excreted primarily by the kidney, dosage should be adjusted in patients with impaired renal function. Caution should be observed in patients with hepatic dysfunction since Ranitidine Tablets is metabolized in the liver.
3. Rare reports suggest that Ranitidine Tablets may precipitate acute porphyric attacks in patients with acute porphyria. Ranitidine Tablets should therefore be avoided in patients with a history of acute porphyria.

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

DRUG INTERACTIONS
Ranitidine has been reported to affect the bioavailability of other drugs through several different mechanisms such as competition for renal tubular secretion, alteration of gastric pH and inhibition of cytochrome P450 enzymes.
Procainamide: Ranitidine, a substrate of the renal organic cation transport system, may affect the clearance of other drugs eliminated by this route. High doses of ranitidine have been shown to reduce the renal excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs. Although this interaction is unlikely to be clinically relevant at usual ranitidine doses, it may prudent to monitor for procainamide toxicity when administered with oral ranitidine at a dose exceeding 300 mg per day.
Warfarin: There have been reports of altered prothrombin time among patients on concomitant warfarin and ranitidine therapy. Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.
Ranitidine may alter the absorption of drugs in which gastric pH is an important determinant of bio-availability. This can result in either an increase in absorption (e.g., triazolam, midazolam, glipizide) or a decrease in absorption (e.g., ketoconazole, Atazanavir, delavirdine, gefitinib). Appropriate clinical monitoring is recommended.
Atazanavir: Atazanavir absorption may be impaired based on known interactions with other agents that increase gastric pH. Use with caution. see atazanavir label for specific recommendations.
Delavirdine: Delavirdine absorption may be impaired based on known interactions with other agents that increase gastric pH. Chronic use of H_2-receptor antagonists with delavirdine is not recommended.
Gefitinib: Gefitinib exposure was reduced by 44% with the co-administration of ranitidine and sodium bicarbonate (dosed to maintain gastric pH above 5.0). Use with caution.
Glipizide: In diabetic patients, glipizide exposure was increased by 34% following a single 150 mg dose of oral ranitidine. Use appropriate clinical monitoring when initiating or discontinuing ranitidine.
Ketoconazole: Oral ketoconazole exposure was reduced by up to 95% when oral ranitidine was co-administered in a regimen to maintain a gastric pH of 6 or above. The degree of interaction with usual dose of ranitidine (150 mg twice daily) is unknown.
Midazolam: Oral midazolam exposure in 5 healthy volunteers was increased by up to 65% when administered with oral ranitidine at a dose of 150 mg twice daily. However, in another interaction trial in 8 volunteers receiving IV midazolam, a 300 mg oral dose of ranitidine increased midazolam exposure by about 9%. Monitor patients for excessive or prolonged sedation when ranitidine is co-administered with oral midazolam.
Triazolam: Triazolam exposure in healthy volunteers was increased by approximately 30% when administered with oral ranitidine at a dose of 150 mg twice daily. Monitor patients for excessive or prolonged sedation.

USE IN SPECIAL POPULATIONS
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. 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 is secreted in human milk. Caution should be exercised when Ranitidine Tablets is administered to a nursing mother.
Pediatric Use: The safety and effectiveness of Ranitidine Tablets 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 in this age group is supported by adequate and well-controlled studies in adults, as well as additional pharmacokinetic data in pediatric patients and an analysis of the published literature.
Safety and effectiveness in pediatric patients for the treatment of pathological hypersecretory conditions or the maintenance of healing of erosive esophagitis have not been establishment.
Safety and effectiveness in neonates (less than 1 month of age) have not been established.
Geriatric Use: Of the total number of subjects enrolled in US and foreign controlled clinical trials of oral formulations of Ranitidine Tablets, 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.

UNDESIRABLE EFFECTS
The following have been reported as events in clinical trials or in the routine management of patients treated with Ranitidine Tablets. The relationship to therapy with Ranitidine Tablets has been unclear in many cases. Headache, sometimes severe, seems to be related to administration of Ranitidine Tablets.
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 atleast twice the pretreatment levels in 6 of 12 subjects receiving 100 mg intravenously 4 times daily for 7 days, and in 4 of 24 subjects receiving 50 mg intravenously 4 times daily for 5 days.
Musculoskeletal: Rare reports of arthralgias and myalgias.
Hematologic: Blood count changes (leukopenia, granulocytopenia, and thrombocytopenia) have occurred in few patients. These were usually reversible. Rare cases of agranulocytosis, pancytopenia, sometimes with narrow 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 and no antiadrenogenic activity, and cimetidine-induced gynecomastia and impotence in hypersecretory patients have resolved when Ranitidine Tablets has been substituted.
However, occasional cases of impotence and loss of libido have been reported in male patients receiving Ranitidine Tablets, 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 (H_2RAs) compared with patients who had stopped H_2RA treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07 – 2.48). However, a casual relationship between use of H_2RAs and pneumonia has not been established.
Other: Rare cases of hypersensitivity reactions (e.g., bronchospasm, fever, rash, eosinophilia), anaphylaxis, angioneurotic edema, acute interstitial nephritis, and small increases in serum creatinine.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Kindly report any suspected adverse reactions to pharmavigil@jbpharma.com

OVERDOSE
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. 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, in excess of 225 mg/kg/day have shown muscular tremors, vomiting, and rapid respiration. Single oral doses of 1,000 mg/kg in mice and rats were not lethal. Intravenous LD_{50}, values in mice and rats were 77 and 83 mg/kg, respectively.

PHARMACODYNAMIC AND PHARMACOKINETIC PROPERTIES
Pharmacodynamics
Ranitidine Tablets is a competitive, reversible inhibitor of the action of histamine at the histamine H_2-receptors, including receptors on the gastric cells. Ranitidine Tablets does not lower serum Ca^{++} in hypercalcemic states. Ranitidine Tablets is not an anticholinergic agent.

Pharmacokinetics
Absorption: Ranitidine Tablets 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, 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 Tablets.
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·**
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 occur in about 3 hours.
Pediatrics: **There are no significant differences in the pharmacokinetic parameter values for ranitidine in** pediatric patients (from one-month up to 16 yrs of age) and healthy adults when correction is made for body weight. The average bioavailability of Ranitidine is given orally to pediatric patients is 48%, which is comparable to the bioavailability of Ranitidine in the adult population. All other pharmacokinetic parameter values (t1/2, V_d, and CL) are similar to those observed with intravenous Ranitidine use in pediatric patients. Estimates of Cmax and Tmax 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

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.
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 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 inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, betazole, and pentagastrin, as shown in below table 2.

Table 2. Effect of Oral Ranitidine Tablets on Gastric Acid Secretion

	Time After Dose, hours	% 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 basal-, nocturnal-, and betazole- stimulated secretions are most sensitive to inhibition by Ranitidine Tablets 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 Tablets 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 has no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum Gastrin: Ranitidine Tablets has little or no effect on fasting or postprandial serum gastrin.
Other Pharmacologic Actions:
1. Gastric bacterial flora-increase in nitrate-reducing organisms, significance not known.
2. Prolactin levels-no effect in recommended oral or IV dosage, but small, transient, dose-related increases in serum prolactin have been reported after IV bolus injections of 100 mg or more.
3. Other pituitary hormones-no effect on serum gonadotropins, TSH or GH. Possible impairment of vasopressin release.
4. No change in cortisol, aldosterone, androgen or estrogen levels.
5. No anti androgenic action.
6. No effect on count, motility or morphology of sperm.

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

Preclinical Safety Data:
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/day.
Ranitidine was not mutagenic in standard bacterial tests (*Salmonella, Escherichia coli*) for mutagenecity 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.

STORAGE
Store in a cool, dry place. Protect from light & moisture.

PRESENTATION
Rantac 150 - Strip pack of 30 tablets
Rantac 300 - Strip pack of 30 tablets

SHELF-LIFE
18 months

INCOMPATIBILITIES
Not Applicable

Marketed by & ® Regd. Trade Mark of :
J. B. CHEMICALS & PHARMACEUTICALS LTD.
Neelam Centre, 'B' Wing, Hind Cycle Road, Worli, Mumbai – 400 030. India.

Note: This prescribing information is applicable for India Market only.

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