

PRODUCT MONOGRAPH

**RANITIDINE NON PRESCRIPTION**

Ranitidine (as Ranitidine hydrochloride) Tablets BP

150 mg

Histamine H<sub>2</sub> Receptor Antagonist

Sandoz Canada Inc.  
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## RANITIDINE NON PRESCRIPTION

Ranitidine (as Ranitidine hydrochloride) Tablets BP

### PART I: HEALTH PROFESSIONAL INFORMATION

#### SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet 150 mg	None <i>For a complete listing see Dosage Forms, Composition and Packaging section.</i>

#### INDICATIONS AND CLINICAL USE

RANITIDINE NON PRESCRIPTION tablets are indicated for:

- fast and effective relief, treatment, and prevention, day or night, of the burning and discomfort of acid indigestion (dyspepsia), heartburn, hyperacidity, sour stomach, and upset stomach associated with excess stomach acid.

These symptoms may be brought on by consuming food and beverages.

#### CONTRAINDICATIONS

RANITIDINE NON PRESCRIPTION (ranitidine hydrochloride) is contraindicated for patients known to have hypersensitivity to any component of the preparation. RANITIDINE NON PRESCRIPTION should not be administered to patients with a history of hypersensitivity to other histamine H<sub>2</sub>-receptor antagonists. For a complete listing, see the Dosage Forms, Composition and Packaging section of the product monograph. See also Warnings and Precautions.

#### WARNINGS AND PRECAUTIONS

##### Gastrointestinal

Treatment with a histamine H<sub>2</sub>-antagonist may mask symptoms associated with carcinoma of the stomach and, therefore, may delay diagnosis of that condition. Accordingly, patients should be advised to consult a physician if they have difficulty or pain on swallowing, experience choking or persistent abdominal discomfort or if symptoms get worse or persist for more than 2 weeks or new symptoms develop.

## **Renal**

Ranitidine is excreted via the kidneys and, in the presence of severe renal impairment, plasma levels of ranitidine are increased and elimination prolonged. Accordingly, ranitidine should be used under physician supervision for these patients.

## **Hematologic**

Rare clinical reports suggest that ranitidine may precipitate acute porphyric attacks. Therefore, ranitidine should be avoided in patients with a history of acute porphyria.

## **Special Populations**

**Pregnant Women:** The safety of ranitidine in the treatment of conditions where a controlled reduction of gastric secretion is required during pregnancy has not been established. Reproduction studies performed in rats and rabbits at higher doses have revealed no evidence of ranitidine induced impaired fertility or harm to the fetus. Nevertheless, if the administration of ranitidine is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the fetus.

**Nursing Women:** Ranitidine is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated. Women who are breast feeding are advised to speak with their doctor before taking RANITIDINE NON PRESCRIPTION Tablets.

**Pediatrics (< 16 years of age):** Children under 16 years of age should be supervised by a physician.

**Geriatrics (> 65 years of age):** Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with ranitidine is instituted. Elderly patients receiving NSAIDs concomitantly with ranitidine should be closely supervised. As with all medication, in the elderly, consideration should be given to concurrent drug therapy.

## **ADVERSE REACTIONS**

### **Adverse Drug Reaction Overview**

Ranitidine has been shown to be generally very well tolerated. In various clinical trials involving either 75 mg or 150 mg of ranitidine the adverse reaction rates were comparable with the most frequently reported adverse events being: headache, nausea, vomiting, and diarrhea: common [frequent] >1% and <10%. Overall adverse event incidence among ranitidine-treated subjects was comparable to that seen in placebo-treated subjects, (no statistical difference) independent of demographic characteristics.

The following adverse reactions have been reported as events in clinical trials, in post-marketing surveillance, or in the routine management of patients treated with prescription doses of ranitidine hydrochloride. The majority of these events have been observed following oral administration of higher prescription doses of ranitidine, and a causal relationship to ranitidine has not always been established.

**Central Nervous System:** headache, sometimes severe; malaise; dizziness; somnolence; insomnia; vertigo; dystonia; nervousness; and reversible blurred vision suggestive of a change in

accommodation. Isolated cases of reversible mental confusion, delusion, delirium, mania, agitation, depression, hallucinations have been reported, predominantly in severely ill elderly patients.

**Cardiovascular:** As with other H<sub>2</sub> receptor antagonists, there have been rare reports of arrhythmias such as tachycardia, premature ventricular beats, bradycardia, and atrioventricular block, and very rare reports of blood pressure increases and palpitations.

**Gastrointestinal:** Constipation, diarrhea, nausea/vomiting, abdominal discomfort/pain, dysgeusia, and dry mouth. Rebound hypersecretion has been reported upon withdrawal of ranitidine therapy.

**Hepatic:** Transient and reversible changes in liver function tests can occur (increase in ALT and AST values). With oral administration, there have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed with or without jaundice and cholestatic jaundice. In such circumstances, ranitidine should be discontinued immediately. These are usually reversible, but in exceedingly rare circumstances, death has occurred.

**Musculoskeletal:** Rare reports of arthralgia and myalgia and very rare reports of asthenia.

**Haematologic:** Blood count changes (anemia, leukopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible. Rare cases of agranulocytosis, pancytopenia, or neutropenia, sometimes with marrow hypoplasia or aplasia have been reported.

**Endocrine:** No clinically significant interference with endocrine or gonadal function has been reported. There have been rare reports of breast symptoms in men taking ranitidine.

**Dermatologic:** Pruritis, rash, including cases suggestive of mild erythema multiforme. Alopecia, contact dermatitis, photosensitivity.

**Other:** Rare cases of hypersensitivity reactions (including angina, chest pain, bronchospasm, fever, rash, eosinophilia, anaphylaxis, urticaria, angioneurotic edema, hypotension) and small increases in serum creatinine have occasionally occurred after a single dose. Acute pancreatitis, meningitis, nephrotoxicity has been reported rarely. Rare cases of reversible involuntary motor disturbances and intraocular pressure changes have been reported.

## DRUG INTERACTIONS

### Overview

Although ranitidine has been reported to bind weakly to cytochrome P<sub>450</sub> *in vitro*, recommended doses of the drug do not inhibit the action of the hepatic cytochrome P<sub>450</sub>-linked oxygenase enzymes. A review of selected publications of controlled clinical drug interaction studies, at the level of hepatic elimination has indicated ranitidine is unlikely to cause clinically significant potentiation of actions of drugs which are inactivated by the hepatic cytochrome P<sub>450</sub> enzyme system; these drugs may include: diazepam, phenytoin, propranolol, theophylline, and warfarin.

Sporadic cases (approximately 1 case per 4 million patient treatments) of drug interactions have been reported in elderly patients involving both hypoglycaemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials have not shown interactions. These reports are based on use for prescription indications and dosage.

Patients consuming NSAIDs may have dyspepsia as a side effect of these medicines and should consult a physician or a pharmacist before taking RANITIDINE NON PRESCRIPTION.

### **Drug-Drug Interactions**

**Antacids:** concurrent administration of high-dose antacids (75 mEq) with ranitidine is not recommended. The absorption of ranitidine may be decreased. Patients should be cautioned not to take antacids within ½ to 1 hour of ranitidine ingestion.

**Sucralfate:** if high doses of sucralfate (two grams) are co-administered with ranitidine, the absorption of ranitidine may be reduced. This effect is not seen if sucralfate is taken at least two hours after ranitidine administration. These reports are based on use of prescription indications and dosage.

**Procainamide:** ranitidine is believed to compete for active renal tubular secretion and/or inhibit the absorption of procainamide. Data indicates adjustment of procainamide doses in the elderly, patients with renal insufficiency, and patients receiving high doses of ranitidine is warranted. These reports are based on use for prescription indications and dosage.

Interactions with the following drugs have been reported with prescription strength ranitidine: Alendronate, amoxicillin, clavulanic acid, cefditoren, cefpodoxime, ceftibuten, delavirdine, dicumarol, diltiazem, enoxacin, fluvastatin, fosphenytoin, gefitinib, glyburide, itraconazole, metformin, midazolam, miglitol, nisoldipine, pancreatin, pancrelipase, pancuronium, pentoxifylline, sucralfate, tolazoline, triamterene, triazolam, tubocurarine.

**Triazolam:** In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were higher during BID 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 (alpha)-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.

**Ethanol:** Consumption of moderate amounts of alcohol is unlikely to result in clinically important alterations in blood alcohol concentrations and/or alcohol metabolism. The co-administration of a single oral dose of ranitidine 75 mg and ethanol 0.15 g/Kg has no clinically relevant effect on ethanol pharmacokinetics as shown in a double-blind placebo-controlled, crossover study in 25 healthy subjects.

Use of ranitidine may result in clinically important interactions if administered together with other medications. Ranitidine should only be administered concomitantly with the following drugs under medical supervision:

**Ketoconazole:**

Concomitant use of ranitidine and ketoconazole results in significantly reduced absorption of ketoconazole and increased absorption of ranitidine.

**Tolazoline:**

Concomitant use of ranitidine significantly impairs the effect of tolazoline.

**Atazanavir:**

Ranitidine significantly reduces the absorption of atazanavir.

## **DOSAGE AND ADMINISTRATION**

### **Dosing Considerations**

- Patients with severe renal impairment should only use this product under physician supervision.
- Patients should be cautioned not to take antacids within ½ to 1 hour of this product.
- Patients taking NSAIDs may have dyspepsia as a side effect and so should consult their physician before initiating therapy with RANITIDINE NON PRESCRIPTION
- Patients should be advised to stop use and consult their physician if symptoms get worse or continue or new symptoms develop after 14 days of treatment.

### **Recommended Dose and Dosage Adjustment**

**Adults and children 16 years of age and older:** One tablet should be taken when symptoms appear, day or night. If symptoms persist for more than 1 hour or return after 1 hour, a second tablet may be taken.

For prevention of symptoms brought on by consuming food or beverages, 1 tablet should be taken 30 to 60 minutes before eating a meal or consuming beverages expected to cause symptoms.

Tablet should be swallowed whole with water. The maximum dosage is 2 tablets (300 mg for the 150 mg strength tablet) in a 24 hour period. Patients are advised to stop use and consult their physician if symptoms get worse or continue or new symptoms develop after 14 days of treatment.

**Children under 16 years of age:** Children under 16 years of age should be supervised by a physician.

**Elderly:** No dosage adjustment is required in the elderly. Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with RANITIDINE NON PRESCRIPTION is instituted. Elderly patients receiving NSAIDs concomitantly with RANITIDINE NON PRESCRIPTION should be closely supervised. As with all medication, in the elderly, consideration should be given to concurrent drug therapy.

## OVERDOSAGE

There is no experience to date with deliberate overdosage. The usual measures to remove unabsorbed drug from the gastrointestinal tract (including activated charcoal or syrup of ipecac), clinical monitoring and supportive therapy should be employed. Also, if need be, the drug can be removed from the plasma by haemodialysis. Up to 6 g per day has been administered without untoward effect.

For management of a suspected drug overdose contact your regional Poison Control Centre immediately.

## ACTION AND CLINICAL PHARMACOLOGY

### **Mechanism of Action**

Ranitidine is an antagonist of histamine at gastric H<sub>2</sub>-receptor sites. Thus, ranitidine inhibits both basal gastric secretion and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. Inhibition of gastric acid secretion has been observed following intravenous, intraduodenal and oral administration of ranitidine. This response is dose-related, a maximum response being achieved at an oral dose of 300 mg/day.

Pepsin secretion is also inhibited but secretion of gastric mucus is not affected. Ranitidine does not alter the secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancreozymin.

### **Pharmacodynamics**

Ranitidine is rapidly absorbed after oral administration, peak plasma concentrations being achieved within 2 to 3 hours. These plasma concentrations are not significantly influenced by the presence of food in the stomach at the time of the oral administration nor by regular doses of antacids.

Bioavailability of oral ranitidine is approximately 50%. Serum protein binding of ranitidine in man is in the range 10 to 19%. The elimination half-life is approximately 3 hours. The principal route of excretion is the urine (40% recovery of free and metabolized drug in 24 hours).

There is a significant linear correlation between the dose administered and the inhibitory effect upon gastric acid secretion for single oral doses up to 300 mg. In healthy subjects a single 75 mg dose of ranitidine significantly reduced meal-stimulated intragastric acidity ([H<sup>+</sup>] AUC) compared with placebo. The effect of ranitidine on intragastric acidity and pH is also dose related.

The important pharmacologic activity of ranitidine is inhibition of gastric acid and fluid secretion in basal and stimulated states, which increases the pH and decreases the volume of secretions. A single 75 mg dose, compared to placebo, has an early onset of action; significantly elevating gastric pH within one hour, and lasting for up to 13 hours post dosing. After correcting for onset of action (within one hour), the duration of acid suppression for ranitidine 75 mg is up to 12 hours (i.e. all day or all night). In the same multicentre, randomized, cross-over study, the onset of acid suppression effect for ranitidine 75 mg was statistically superior to famotidine 10 mg at only one and two hours

post-dosing. The duration and degree of acid suppression of ranitidine 75 mg (63.1%, n=75) were superior to cimetidine 200 mg (37.8%, n=52) over the 10 hour daytime evaluation period.

**Table 1. Summary of weighted mean hydrogen ion activity (H<sup>+</sup>AUC mmol/L.h)**

Time Period	Placebo N=75 subjects	Ranitidine 75 mg N=75 subjects	Cimetidine 200 mg N=52 subjects	Famotidine 10 mg N=22 subjects
Total (20-h)	30.89	18.21*†	25.08*	19.32*
Day (11.00h- 22.30h)	32.76	18.19*†	22.06*	13.23*
Night (22.30h- 08.30h)	28.83	23.23*†	28.09	25.41*

\* p<0.05 compared with paired placebo group

† p<0.05 compared with paired cimetidine group

**Table 2. Changes in intragastric acidity and pH**

	Median percentage decrease in acidity			Median intragastric pH	
	total	day <sup>a</sup>	night <sup>a</sup>	day <sup>a</sup>	night <sup>a</sup>
Ranitidine 75mg (N=75)	44.1%†	63.1%†	21.2%†	2.10*	1.80*
Famotidine 10mg (N=22)	38.9%	58.9%	20.1%	2.06*	1.90
Cimetidine 200mg (N=52)	23.0%	37.8%	1.8%	1.69*	1.77
Placebo (N=75)				1.48	1.70

\* p<0.05 compared with paired placebo group

† p<0.05 compared with paired cimetidine group

<sup>a</sup> day=12.30h to 22.30h; night=22.30h to 8.30h

In a large, multicentre, dose-ranging, placebo-controlled trial in patients with episodic heartburn, a single 75 mg dose relieved symptoms within 30 minutes and provided relief for the duration of the 4 hour evaluation period.

Volunteers treated with an oral dose of ranitidine have reported no significant gastrointestinal or central nervous system side effects; moreover pulse rate, blood pressure, electrocardiogram and electroencephalogram are not significantly affected in man following ranitidine administration. In healthy human volunteers and patients, ranitidine, when administered orally did not influence plasma levels of the following hormones: cortisol, testosterone, oestrogens, growth hormone, follicle-stimulating hormone, luteinizing hormone, thyroid-stimulating hormone, aldosterone or

gastrin; although like cimetidine, ranitidine reduced vasopressin output. Treatment for up to 6 weeks with ranitidine 150 mg twice daily by mouth did not affect the human hypothalamic-pituitary-testicular-ovarian or -adrenal axes.

The safety and efficacy of 75 mg ranitidine for treatment of episodic heartburn were established in two large replicate Phase III studies involving 2985 patients. These two pivotal studies demonstrated that one ranitidine 75 mg tablet was statistically and clinically superior to placebo in providing relief of episodic heartburn beginning at 30 minutes.

In two subsequent heartburn treatment trials evaluating total pain relief, both the 75 mg and 150 mg strengths of ranitidine were demonstrated to be statistically significantly superior to placebo as shown in the table below.

Table 3 presents pooled data for the primary efficacy variable of total pain relief for the first treated episode (TOTPAR) along with its associated p values.

**Table 3. Pooled Treatment Data Primary Variable (Intent-to-treat subjects)**

Efficacy Variable	Ranitidine 150 mg (N=637)	Ranitidine 75 mg (N=637)	Placebo (N=635)	Ranitidine 75 mg vs placebo (p value)	Ranitidine 150 mg vs placebo <sup>1</sup> (p value)	Ranitidine 150 mg vs Ranitidine 75 mg (p value)
TOTPAR for 1 <sup>st</sup> drug treated episode (mean)	20.8	20.4	18.3	<0.001	0.004	0.673

The safety and efficacy of 150 mg ranitidine for the prevention or reduction of severity of meal induced heartburn when taken immediately before consuming food and beverages anticipated to provoke heartburn was studied in two pivotal and one supporting large replicate Phase III well controlled, multi-center, double-blind, randomized, placebo-controlled studies involving 2484 patients. The results of the 2 pivotal and supporting studies are summarized below.

**Table 4. Pooled Prevention Data for Key Efficacy Variables (Intent-to-Treat Subjects) Pivotal Studies**

Efficacy Variable	Ranitidine 150 mg (N=518)	Ranitidine 75 mg (N=524)	Placebo (N=521)
Treatment Meal AUC (mm·hr)	87.0 ± 3.96*†	91.1 ± 3.84* <sup>a</sup>	107.5 ± 4.17
Reduction in Treatment Meal AUC (%)	49.1 ± 2.44*	44.0 ± 2.29* <sup>b</sup>	32.7 ± 2.93
Treatment Meal peak heartburn severity (mm)	40.2 ± 1.29*	41.6 ± 1.23* <sup>c</sup>	47.0 ± 1.28
Peak heartburn reduction (%)	42.6 ± 1.78*	38.7 ± 1.73* <sup>d</sup>	31.2 ± 1.79

<sup>1</sup>

Largest consecutive time points with no heartburn	5.3 ± 0.24*	4.7 ± 0.23	4.2 ± 0.22
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\*p<0.05 versus placebo, †p<0.05 versus ranitidine 75 mg, <sup>a</sup>N=520, <sup>b</sup>N=518, <sup>c</sup>N=521, <sup>d</sup>N=519

**Table 5. Prevention Data for Key Efficacy Variables (Intent-to-Treat Subjects) Supporting Study**

Efficacy Variable	Ranitidine 150 mg (N=306)	Ranitidine 75 mg (N=309)	Placebo (N=306)
Treatment Meal AUC (mm·hr)	94.6 ± 5.91	88.6 ± 4.97	98.8 ± 4.83
Reduction in Treatment Meal AUC (%)	45.4 ± 3.08	43.4 ± 3.20	39.2 ± 3.05
Treatment Meal peak heartburn severity (mm)	42.4 ± 1.80	43.4 ± 1.60	46.8 ± 1.61
Peak heartburn reduction (%)	39.7 ± 2.47	37.4 ± 2.30	32.8 ± 2.29
Largest consecutive time points with no heartburn	5.5 ± 0.32*	5.2 ± 0.30	4.4 ± 0.29

\*p<0.05 versus placebo

In pooled data of the 2 studies reflected in Table 4, ranitidine 150 mg was effective in preventing meal-related heartburn. Ranitidine 75 mg was statistically significantly better than placebo for the primary endpoint in one of the 2 pivotal clinical trials and in the pooled analysis, but was less consistently effective than ranitidine 150 mg in the prevention pivotal trials.

### **Pharmacokinetics**

**Absorption:** 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 for up to 12 hours. There is a relationship between plasma concentrations of ranitidine and suppression of gastric acid production but wide interindividual variability exists.

Ranitidine is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring two to three hours after a 150 mg dose. The elimination half-life is 1.5 to 3 hours.

Lower than prescription doses of ranitidine significantly reduce meal-stimulated intragastric acidity in human subjects. The effect is dose-related and acidity declines linearly with increasing doses of ranitidine.

Ranitidine is absorbed very rapidly after an intramuscular injection. Mean peak levels of 576 ng/mL occur within 15 minutes or less following a 50 mg intramuscular dose. Absorption from intramuscular sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous administration.

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

**Metabolism:** The gastric antisecretory activity of ranitidine metabolites has been examined. In man,

both the principal metabolite in the urine, the N-oxide (4% of the dose) and the S-oxide (1%) possess weak H<sub>2</sub>-receptor blocking activity but desmethylranitidine (1%) is only 4 times less potent than ranitidine in the rat and half as potent as ranitidine in the dog.

**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 530 mL/min, indicating active tubular excretion, with a total clearance of 760 mL/min.

**Special Populations and Conditions**

**Hepatic Insufficiency:** 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.

**Renal Insufficiency:** Ranitidine is excreted via the kidneys and, in the presence of severe renal impairment, plasma levels of ranitidine are increased and elimination prolonged. Accordingly, RANITIDINE NON PRESCRIPTION should be used under physician supervision for these patients

**STORAGE AND STABILITY**

Store between 15 and 30°C. Protect from light and moisture.

**DOSAGE FORMS, COMPOSITION AND PACKAGING**

<p>RANITIDINE NON PRESCRIPTION Tablets (150 mg)</p>	<p>Medicinal Ingredients : 168 mg of ranitidine HCl (equivalent to ranitidine anhydrous free base 150 mg).</p>	<p>Nonmedicinal Ingredients: magnesium stearate, microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycolate and colloidal anhydrous silica.</p> <p>Film-coating: lactose, methylhydroxypropylcellulose, titanium dioxide and macrogol 4000.</p>
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RANITIDINE NON PRESCRIPTION is Gluten- and tartrazine-free.

**RANITIDINE NON PRESCRIPTION Tablets:**

Each white, round, biconvex, film-coated tablets with score notch on one side and “R150” on the other, available in blister packs of 30 and 60 and bottles of 100 tablets.

## PART II: SCIENTIFIC INFORMATION

### PHARMACEUTICAL INFORMATION

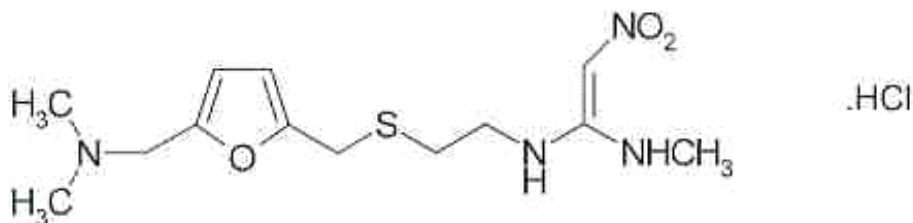
#### DRUG SUBSTANCE

**Proper Name:** ranitidine hydrochloride

**Chemical Name:** (n-{2-[[[5-[(dimethylamino)-methyl]-2-furanyl]-methyl]thio]ethyl}-N'-methyl-2-nitroethene-1,1-diamine, hydrochloride.

**Molecular Formula and Molecular Mass:**  $C_{13}H_{22}N_4O_3S \cdot HCl$  350.87 g/mol (as hydrochloride salt)

#### Structural Formula:



**Physicochemical properties:** Ranitidine Hydrochloride is a white to pale yellow granular substance. At room temperature, ranitidine hydrochloride is soluble in water, methanol, ethanol and chloroform (decreasing order).

## CLINICAL TRIALS

### Comparative Bioavailability Study

A randomized, 2-way crossover study was conducted in healthy volunteers under fasting conditions with RhoXal Ranitidine (currently Sandoz Ranitidine) 300 mg tablets vs the Canadian reference. The drug has shown that the products are bioequivalent (see Table below).

#### Summary table of the comparative bioavailability data

<b>Ranitidine</b> <b>(1 x 300 mg) tablets</b> <b>From measured data (fasting state)</b> <b>Uncorrected for potency</b> <b>Geometric Mean</b> <b>Arithmetic Mean (CV %)</b>				
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Parameter	Test *	Zantac Reference <sup>†</sup>	% Ratio of Geometric Means	Confidence Interval <sup>#</sup>
AUC <sub>T</sub> (ng.h/mL)	6284.83	5914.32	106.3	94.4 – 119.6 %
	6420.4 (20.0)	6093.7 (22.1)		
AUC <sub>I</sub> (ng.h/mL)	6426.05	6064.72	106.0	94.4 – 118.9 %
	6562.9 (20.0)	6249.1 (22.2)		
C <sub>max</sub> (ng/mL)	1270.6000	1186.7058	107.1	93.3 – 122.9 %
	1310.929 (24.2)	1249.501(28.5)		
T <sub>max</sub> <sup>§</sup> (h)	2.900 (20.6)	3.150 (28.7)		
T <sub>½</sub> <sup>§</sup> (h)	2.6096 (14.3)	2.6868 (12.4)		

RhoXal Ranitidine (currently Sandoz Ranitidine)

<sup>†</sup> Zantac (Glaxo Wellcome) purchased in Canada.

<sup>§</sup> For T<sub>max</sub>, T<sub>½</sub>, the arithmetic mean only is presented.

<sup>#</sup> 90 % Confidence Interval for the AUC<sub>T</sub>, AUC<sub>I</sub> and C<sub>max</sub>.

In 6 clinical trials examining the healing of duodenal ulcers in 1500 patients, a dose of 300 mg daily for 4 weeks was found to have an 83% healing rate; however, increasing the dose to 300 mg twice daily gave significantly better results (92% healed at 4 weeks; p<0.001).

## DETAILED PHARMACOLOGY

### Animal Pharmacology

Ranitidine is a potent competitive reversible, selective antagonist of histamine at H<sub>2</sub>-receptors *in vitro* and *in vivo*. Thus, ranitidine antagonized the actions of histamine at H<sub>2</sub>-receptors in the rat isolated uterus and in the guinea pig isolated atrium. Ranitidine is not an anticholinergic agent. On a molar basis, ranitidine is 4 to 5 times more active than cimetidine with a pA<sub>2</sub> value of 7.2. In concentrations 1000 times greater than those required to block H<sub>2</sub>-receptors, it failed to block either H<sub>1</sub>-receptors or muscarinic receptors in the guinea pig isolated ileum. The beta-adrenoceptor responses of the rat uterus and guinea pig atrium to isoprenaline were also unaffected by ranitidine.

Blockade of histamine H<sub>2</sub>-receptors in the stomach *in vivo* is the pharmacological action of ranitidine with greatest immediate clinical relevance. Ranitidine inhibits gastric secretion induced by various secretagogues in both the rat and dog.

In the conscious dog with a Heidenhain pouch, ranitidine given orally or intravenously antagonized gastric acid secretion induced by histamine, pentagastrin and bethanechol. Ranitidine was 5 to 10 times more active than cimetidine. However, both ranitidine and cimetidine had similar time curves of action. Ranitidine also inhibited the gastric secretory response to food in the conscious fistulated dog.

Ranitidine inhibited acid secretion in the perfused stomach of the anaesthetised rat, and acetylsalicylic acid-induced gastric lesion formation in the conscious rat, both in the presence and absence of excess hydrochloric acid. Measurements of the ratio of mucosal blood flow to acid secretion show that the inhibitory action of ranitidine upon gastric acid secretion cannot be attributed to changes in blood flow.

There were no behavioural effects in the mouse and rat after oral administration of 800 mg/kg ranitidine. Cats and dogs dosed with ranitidine 80 mg/kg orally, exhibited no behavioural effects indicative of an action on the central nervous system, although at this high-dose level in the dog there was an indication of peripheral vasodilation and skin irritation due to released histamine. Ranitidine, when co-administered with the following CNS modulating preparations; codeine, hexobarbitone, ethyl alcohol, chlordiazepoxide, chlorpromazine, imipramine,  $\alpha$ -methyl dopa, reserpine, apomorphine or pentylentetrazol, did not alter the pharmacological effects of either preparation.

At a dose level 45 times the antisecretory ED<sub>50</sub>, intravenous infusion of ranitidine had no effect on the heart rate, blood pressure or electrocardiogram of the anaesthetised dog. The respiratory system was unaffected by ranitidine after oral doses in the mouse, rat, rabbit, cat and dog and after intravenous doses in the dog.

In the conscious dog, ranitidine had no appreciable effect on blood pressure or heart rate when administered orally at 10 mg/kg. There were short-lived falls in diastolic blood pressure after an intravenous dose of 10 mg/kg, 370 times the antisecretory dose level. There was no evidence of arrhythmia nor of any electrocardiographic abnormality.

Long-term toxicity studies have shown that ranitidine does not possess antiandrogenic activity nor does it displace dihydrotestosterone from the androgen binding sites.

Metoclopramide, atropine, and acetylsalicylic acid in the rat produced no change in the antisecretory activity of ranitidine.

The effect of ranitidine on anti-inflammatory drugs was varied. There was no effect on the anti-inflammatory action of prednisolone, but the anti-inflammatory action of indomethacin was enhanced. Administration of ranitidine reduced the frequency of acetylsalicylic acid- and indomethacin-induced gastric erosions. The antinociceptive action of acetylsalicylic acid was reduced after ranitidine treatment.

Ranitidine, unlike cimetidine, does not inhibit the hepatic mixed function oxygenase system. Spectral interaction studies have shown that whilst cimetidine binds strongly to cytochrome P<sub>450</sub>, ranitidine has only weak affinity for this enzyme. Cimetidine is known to impair the metabolism of pentobarbitone and warfarin. In doses of up to 166 mg/kg in the rat, ranitidine had no effect on the pentobarbitone sleeping time or the pharmacokinetics and pharmacodynamics of warfarin.

### **Metabolism, Distribution and Excretion**

The metabolism of ranitidine hydrochloride has been studied in four species of laboratory animal (mouse, rat, rabbit and dog) using radio-labelled drug. The drug was rapidly absorbed after oral administration. In the mouse, rat and rabbit between 30% and 60% of the administered radioactivity was excreted in the urine, the remainder being recovered in the feces.

In the mouse, 47% was excreted in the urine within 24 hours. In the rat, N-demethylation of ranitidine was the major route of metabolism. 30% of the administered dose was excreted in the urine as unchanged drug, up to 14% as desmethylranitidine, 3-6% as the N-oxide and 4% as the S-oxide. In rat bile the major radioactive components were ranitidine and an unidentified metabolite known as "Fast-Running Metabolite" (FRM) which is thought to be a charge transfer complex of ranitidine with bile pigments.

In the rabbit, sulphoxidation of ranitidine was the major route of metabolism, 18% of the administered dose being excreted in the urine as unmetabolized ranitidine, 8% as S-oxide, 2-4% as the N-oxide, and 2-4% as desmethylranitidine.

In the dog up to 70% of the administered dose was excreted in the first 24 hours. About 40% of the drug was excreted in the urine as unchanged ranitidine and up to 30% as the N-oxide, N-oxidation being the main route of metabolism of ranitidine in the dog. The N-oxide was also the major radioactive component present in dog bile together with small amounts of unchanged ranitidine and FRM.

In the rat, rabbit and dog, less than 10.1% of ranitidine in plasma is protein bound. Within one to seven days of administration of radio-labelled drug in the rat and dog, over 99% of the radioactivity was cleared from the body. In common with many drugs, radioactivity persisted in the uveal tract of these two species, the half-life in the dog uveal tract being of the order of 6 months. Ranitidine and its S-oxide have greater affinity for melanin than the desmethyl metabolite; the N-oxide is bound only to a small extent.

The placental transfer of radioactive ranitidine and its metabolites has been studied in the pregnant

rat and rabbit. Whole body autoradiography of rat and rabbit fetuses showed that small amounts of radioactivity were present in the uveal tract of the fetal eye in both species, in the gall bladder and intestine of the rabbit fetus and in the bladder of the rat fetus. Radioactivity was also detected in the salivary and mammary glands of the maternal rat and at very low concentration, in the milk.

### **Human Pharmacokinetics**

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 for up to 12 hours. There is a relationship between plasma concentrations of ranitidine and suppression of gastric acid production but wide interindividual variability exists.

Lower than prescription doses of ranitidine significantly reduce meal-stimulated intragastric acidity in human subjects. The effect is dose-related and acidity declines linearly with increasing doses of ranitidine.

Ranitidine is 50% absorbed after oral administration compared to an IV injection with mean peak levels of 440 to 545 ng/mL occurring two to three hours after a 150 mg dose. The elimination half-life is 1.5 to 3 hours.

The pharmacokinetics of lower doses of ranitidine have also been studied. Peak plasma concentrations and AUC showed a linear relationship over the dose range 20-80mg;  $T_{max}$ ,  $t_{1/2}$  and clearance were independent of dose.

Ranitidine is absorbed very rapidly after an intramuscular injection. Mean peak levels of 576 ng/mL occur within 15 minutes or less following a 50 mg intramuscular dose. Absorption from intramuscular sites is virtually complete, with a bioavailability of 90% to 100% compared with intravenous administration.

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 530 mL/min, indicating active tubular excretion, with a total clearance of 760 mL/min. The volume of distribution is 1.4 L/kg. Serum protein binding averages 15%.

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.

The gastric antisecretory activity of ranitidine metabolites has been examined. In man, both the principal metabolite in the urine, the N-oxide (4% of the dose) and the S-oxide (1%) possess weak H<sub>2</sub>-receptor blocking activity but desmethylranitidine (1%) is only 4 times less potent than ranitidine in the rat and half as potent as ranitidine in the dog.

## **TOXICOLOGY**

### **Animals**

#### **Toxicology, Impairment of Fertility, Carcinogenesis and Mutagenesis**

Ranitidine hydrochloride has been subjected to exhaustive toxicological testing which has

demonstrated the lack of any specific target organ or any special risk associated with its clinical use.

### **Acute Toxicity Studies**

In mice and rats, the intravenous LD<sub>50</sub> is of the order of 75 mg/kg, whereas orally, even doses of 1000 mg/kg are not lethal. In dogs, the oral minimum lethal dose is 450 mg/kg/day. High single doses of ranitidine (up to 80 mg/kg orally) show only minimal and reversible signs of toxicity, some of which are related to transitory histamine releases.

### **Long-Term Toxicity Studies**

In the long-term toxicity and carcinogenicity studies, very high doses of ranitidine were given daily to mice (up to 2000 mg/kg/day) throughout their normal life-span, and to dogs (up to 450 mg/kg/day) for periods of up to one year.

These doses produced massive plasma ranitidine concentrations far in excess of those found in human patients receiving ranitidine at the recommended therapeutic dose. For example, in the dogs, peak plasma concentrations were in excess of 115 mcg/mL and in mice basal plasma levels were in the range of 4-9 mcg/mL. In man, after oral administration of 150 mg ranitidine, the mean peak plasma concentration (C<sub>max</sub>) was between 360 and 650 ng/mL. In the rat, doses as high as 2000 mg/kg/day were well tolerated, the only morphological change seen was the increased incidence of accumulations of foamy alveolar macrophages in the lungs. The accumulations of these cells is a natural phenomena in aging rats and chronic administration of a wide variety of drugs has been known to contribute to this process. Therefore, it is unlikely that the pharmacologic concentrations of ranitidine administered to these rats contributed to this natural process.

In the six-week and six-month oral studies in the dog (100 mg/kg/day) loose feces were occasionally detected, while in the six-month study loose stools were accompanied on eight occasions by mucus-like material and sometimes by blood, mostly from one dog. Loose feces, salivation and vomiting were observed in the 54-week dog study.

In isolated cases, dogs passed red-stained feces which occasionally tested positive for occult blood. When the dose level was increased from 100 mg/kg/day to 225-450 mg/kg/day, no further red-stained feces were seen, suggesting that any relationship to ranitidine is unlikely. Postmortem examination of the dogs revealed no ranitidine-induced changes in the alimentary tract.

One dog had marginally raised levels of plasma alanine aminotransferase and alkaline phosphatase during the six-week study. This same dog also showed some necrotic foci in the liver. Small lesions of focal necrosis and fibrosis were also seen in one piece of liver from one female dog treated with 100 mg/kg for six months. No other differences were detected by light and electron microscopic examination of the treated and control livers. Since the focal lesions were seen in only one dog and were restricted to one piece of liver, it suggests that they were not caused by ranitidine.

Muscular tremors, an inability to stand, and rapid respiration were seen on occasion in dogs treated with 225 mg/kg/day in the 54-week study. The prevalence of these observations was increased when the dose was increased to a toxic level of 450 mg/kg/day. One dog died; no specific pathological changes or reason for the death was discovered.

Changes in the colour or granularity of the tapetum lucidum of the eye were detected in three dogs

receiving the highest dose of ranitidine (450 mg/kg/day) during the 54-week study. In one dog, this change was considered to be related to treatment. The change, a pallor of the tapetum, was reversible. No changes were seen with light or electron microscopic examination of the eye. The changes in the tapetum are of no clinical significance in humans since (i) humans do not have a tapetum lucidum and (ii) the changes were only seen at toxic pharmacological concentrations of ranitidine.

The mean serum glutamic pyruvic transaminase values for dogs treated at 450 /mg/kg/day were significantly greater, albeit marginally, than the control values. These enzyme increases were not accompanied by any histological changes.

Studies in which ranitidine was administered parenterally were performed. No sign of specific local irritation attributable to ranitidine was detected. In the rat, no biochemical or histopathological changes were observed at intravenous dose levels as high as 20 mg/kg. Specifically, no significant changes were found in the veins or subcutis. Mild lesions in some muscle samples were observed: usually, the cells were basophilic and smaller than normal; and the nuclei were swollen, more numerous, and sometimes had migrated to the centre of the cell. In the rabbit, slight infiltration of the pannicular muscle by mononuclear cells were noted. This minor subcutaneous reaction was uncommon and showed no group-related distribution. There was no apparent difference in irritancy between ranitidine injection and placebo injection. In the rat, intravenous ranitidine at dose levels of 5.0 and 10.0 mg/kg daily for 15 days and 28 days produced no treatment-related changes of biological importance in the hematopoietic system.

In Beagle dogs, intravenous ranitidine injection in doses up to 10 mg/kg/day for 28 and 42 days, produced no drug-related change in circulating erythrocytes or leukocytes and had no adverse effects on the hematopoietic system. No dose-related changes were seen in electrocardiograms of Beagle dogs receiving up to 10 mg/kg ranitidine by intravenous injection. At dosage levels of up to 30 mg/kg, administered twice daily to Beagle dogs for 14 or 15 days, intravenous ranitidine injection produced no changes of biological significance in haematology, clinical chemistry or urinalysis.

No changes were observed in the eyes of dogs (specifically the tapetum lucidum) receiving ranitidine in doses up to 30 mg/kg twice daily for 15 days. At intravenous doses above 1.25 mg/kg, ranitidine injection produced immediate and transient reactions in the Beagle dog. The following reactions were typically produced by the administration of 1.25 mg/kg: bloodshot eyes, closing and watering of eyes, defecation, diarrhea, erythema, flatus, licking of lips, running nose, salivation, subdued behaviour, swallowing, tachycardia, and trembling. The range and severity of the effects was aggravated by increased dosage.

### **Reproduction Studies (Impairment of Fertility)**

Reproduction studies were carried out in the rat and rabbit. Rats were exposed to ranitidine before and during mating, throughout pregnancy, lactation and during the weaning period. No effects on the reproductive process were seen and there was no evidence of an anti-androgenic effect.

A total of 2297 fetuses from rats treated with ranitidine were examined. There was no evidence that ranitidine is a rat teratogen. Cleft palates occurred in fetuses from both treatment groups, however, there were significantly more in the control rat population.

A total of 944 fetuses from rabbits treated with ranitidine were examined; no drug-related adverse

events or abnormalities in the fetuses were observed.

Rabbits receiving a bolus intravenous injection of ranitidine (10 mg/kg) once daily on gestation days 7-16 exhibited a reduction in weight gain. Their fetuses weighed significantly less than fetuses of untreated controls. In addition, 12.4% of ranitidine-exposed fetuses had cleft palates. Reanalysis of this and a comparison study performed to assess reproducibility demonstrated a lack of data reproducibility. Therefore, the effects observed in the first trial are aberrant, and should not form the basis for maternal or fetal toxicity.

In the subsequent study, no evidence of maternal or fetal toxicity was observed in rabbits dosed with 100 mg/kg ranitidine orally during days 2-29 of pregnancy. The peak plasma levels of ranitidine after a 100 mg/kg oral dose are similar to those obtained one minute after a 10 mg/kg dose administered intravenously (20-25 mcg/mL). Therefore, no teratogenic effects of ranitidine have been demonstrated at doses of 10 mg/kg (IV) and 100 mg/kg (Tablets) in rabbits.

### **Carcinogenicity Studies**

There is no evidence that ranitidine is a carcinogen. Long-term toxicity and carcinogenicity studies have involved the treatment of 600 mice and 636 rats at doses up to 2000 mg/kg for two years and 129 weeks respectively and 42 dogs at doses up to 450 mg/kg/day for periods up to one year. These dose levels are far in excess of those to be used therapeutically in man. None of these animals had any intestinal metaplasia. There was no evidence of a tumourigenic effect of ranitidine in any other tissue.

### **Mutagenesis**

Ranitidine is not mutagenic at doses as great as 30 mg/plate in the Ames Assay utilizing *Salmonella typhimurium* (TA 1538, TA 98, TA 100 and TA 1537) or in doses of 9 mg/plate utilizing *Escherichia Coli* (WP2 and WP2 uvrA) with or without activation.

Ranitidine at concentrations of 20-30 mg/plate had a weak direct mutagenic action in *S. typhimurium* TA 1535 and at 9 mg/plate in *E. coli* WP67. Ranitidine was not mutagenic at a concentration of 2 mg/mL in *E. coli* or *S. typhimurium* in the more sensitive oral solution microtitre fluctuation assay method. This weak direct mutagenic effect is of no clinical significance; the magnitudes of ranitidine concentration used in these assays are thousands of times greater than that attained therapeutically in human plasma.

The principal metabolites of ranitidine in man were not significantly mutagenic. This conclusion is supported by the following experiment. A test solution obtained by interacting ranitidine (10mM) and sodium nitrite (40mM) was mutagenic in *S. typhimurium* (TA 1535) but not in *S. typhimurium* (TA 1537) or in *E. coli* (WP67 or WP2 uvrA). This positive result is attributable to the presence of a nitrosonitrolic acid derivative AH 23729, which was mutagenic. When the sodium nitrite concentration was reduced to 15 mM or less, the solution was not mutagenic in any of the test microorganisms. The formation of AH 23729 requires concentrations of nitrous acid far in excess of those encountered in any probable physiological conditions. The other nitrosation products were not mutagenic in any of the microorganisms tested. There is no reason, therefore, for supposing that ranitidine is likely to be mutagenic in animals or man as a consequence of nitrosation in the stomach.

There is no evidence from long-term toxicology, carcinogenicity and mutagenicity studies in animals

to suggest that ranitidine is likely to have any deleterious effects in man when administered at therapeutic dose levels.

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**PART III: CONSUMER INFORMATION****RANITIDINE NON PRESCRIPTION  
Ranitidine Tablets BP**

**This leaflet is part III of a three-part "Product Monograph" published when RANITIDINE NON PRESCRIPTION was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about RANITIDINE NON PRESCRIPTION. Contact your doctor or pharmacist if you have any questions about the drug.**

**ABOUT THIS MEDICATION****What the medication is used for:**

RANITIDINE NON PRESCRIPTION is a commonly used acid reliever prescribed by doctors world-wide. RANITIDINE NON PRESCRIPTION is a product which contains the maximum nonprescription strength (150 mg) of ranitidine.

RANITIDINE NON PRESCRIPTION provides fast relief, treatment and prevention, day or night, from the burning and discomfort of the following symptoms caused by too much acid in the stomach:

- Heartburn,
- Acid Indigestion,
- Upset or Sour Stomach

**What it does:**

RANITIDINE NON PRESCRIPTION works by reducing and controlling the amount of acid in your stomach for up to 12 hours, day or night. This is what makes RANITIDINE NON PRESCRIPTION different from antacids which only neutralise the acid in your stomach. Antacids do not reduce the production of excess stomach acid.

RANITIDINE NON PRESCRIPTION can also effectively prevent symptoms of heartburn and acid indigestion when taken 30 to 60 minutes before eating food and/or drinking beverages that cause heartburn.

**When it should not be used:**

Do not use RANITIDINE NON PRESCRIPTION if you are allergic to any component of this product or have had an allergic reaction to another product that contains an acid reducer.

**When you should contact your doctor:**

Contact your doctor if the following occur while taking or before taking RANITIDINE NON PRESCRIPTION as the following may be symptoms of a serious reaction/medical condition:

- if you experience heartburn with light-headedness, sweating, dizziness, or frequent wheezing
- if you have chest or shoulder pain with shortness of breath, sweating, pain spreading to neck, arms, or shoulders

**What the medicinal ingredient is:**

Each RANITIDINE NON PRESCRIPTION tablet contains 150 mg of ranitidine, as ranitidine hydrochloride.

**What the important nonmedicinal ingredients are:**

Non-medicinal ingredients: magnesium stearate, microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycolate and colloidal anhydrous silica. The film-coating suspension contains: lactose, methylhydroxypropyl-cellulose, titanium dioxide and macrogol 4000.

RANITIDINE NON PRESCRIPTION is Gluten- and tartrazine-free.

**What dosage forms it comes in:**

Tablets: 150 mg

**WARNINGS AND PRECAUTIONS**

**BEFORE you use RANITIDINE NON PRESCRIPTION talk to your doctor or pharmacist if you:**

- have a stomach or duodenal ulcer
- are taking a prescription medicine for stomach ulcer or any other prescription drugs
- have kidney disease
- have chest pain
- have difficulty or pain on swallowing, experience choking or continuous stomach pain or discomfort
- are nauseous, have severe vomiting, or have bloody or black stools
- have heartburn that is frequent (> 3 times per week) and/or unusually severe
- have had heartburn for over 3 months
- suffer from porphyria (a rare blood disorder)
- are pregnant, or breast-feeding
- are taking non-steroidal anti-inflammatory drugs (NSAIDs), (because these medicines may be causing your symptoms) or other medications
- experience unintended weight loss
- are over 40 years of age and are experiencing new or recently changed symptoms of heartburn or acid indigestion
- have any other illness, or are taking any prescription medicines, for which you are seeing a doctor regularly
- are under 16 years of age.

**INTERACTIONS WITH THIS MEDICATION**

**BEFORE you use RANITIDINE NON PRESCRIPTION talk to your doctor or pharmacist if:** you are taking antacids, ketoconazole, tolazoline, atazanavir, sucralfate, triazolam and procainamide.

Do not take antacids within 1 hour of taking RANITIDINE NON PRESCRIPTION.

**PROPER USE OF THIS MEDICATION**

**Usual dose:**

Adults and children 16 years and older: swallow one tablet whole with a glass of water when symptoms appear, day or night. If symptoms persist for more than 1 hour or return after 1 hour, a second tablet may be taken.

For prevention of symptoms brought on by consuming food or beverages, 1 tablet should be taken 30 to 60 minutes before eating a meal or consuming beverages expected to cause symptoms.

Do not take more than 2 tablets during a 24 hour period. Stop use and consult your doctor if symptoms get worse or new symptoms develop or persist after 14 days of treatment. RANITIDINE NON PRESCRIPTION and antacids should be taken one hour apart.

**What can you do to help avoid symptoms:**

- do not lie down or bend over soon after eating,
- if you are overweight, try to reduce excess weight,
- if you smoke, stop or cut down,
- avoid or limit foods such as: caffeine (coffee, tea, or cola drinks), chocolate, spicy or fatty fried foods and alcohol,
- try to reduce stress,
- do not eat large meals; eat late at night or before bedtime,
- raise the head of your bed,
- consider wearing loose fitting clothing around abdomen (stomach).

**Overdose:**

In case of drug overdose, contact a health care practitioner, hospital emergency department or regional Poison Control Centre immediately, even if there are no symptoms.

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

Common side effects that have occurred with RANITIDINE NON PRESCRIPTION include headache, nausea, vomiting and diarrhea.

**SERIOUS SIDE EFFECTS, HOW OFTEN THEY HAPPEN AND WHAT TO DO ABOUT THEM**

Symptom / effect	Talk with your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
<b>Rare</b> Hypersensitivity Reaction Raised and itchy rash (hives), swelling, sometimes of the face or mouth (angioedema), chest pain, shortness of breath, unexplained fever, wheezing or difficulty in breathing, feeling faint, especially when standing up, collapse			✓

Very Rare	<b>Serious Skin Reactions</b> Skin rash, which may blister, and look like small targets (central dark spots surrounded by a paler area, with a dark ring around the edge)			✓
	<b>Hepatitis</b> Yellowing of the skin or whites of the eyes, dark or tea coloured urine, pale coloured stools/ bowel movements, nausea/ vomiting, loss of appetite, pain, aching or tenderness on right side below the ribs			✓
	<b>Cardiovascular</b> Slow, fast or irregular heartbeat			✓

*This is not a complete list of side effects. For any unexpected effects while taking RANITIDINE NON PRESCRIPTION, contact your doctor or pharmacist.*

**HOW TO STORE IT**

Keep in a safe place out of the reach of children. Store between 15 and 30° C. Protect from light and excessive moisture.

**Reporting Side Effects**

You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.

**3 ways to report:**

- Online at [MedEffect](#);
- By calling 1-866-234-2345 (toll-free);
- By completing a Consumer Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program  
Health Canada, Postal Locator 0701E  
Ottawa, ON  
K1A 0K9

Postage paid labels and the Consumer Side Effect Reporting Form are available at [MedEffect](#).

*NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.*

**MORE INFORMATION**

This document plus the full product monograph, prepared for health professionals can be obtained by contacting the sponsor, Sandoz Canada Inc. at:  
1-800-361-3062

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