Ranitidine Syrup
(Ranitidine Oral Solution, USP)

15 mg/mL
(75 mg/5 mL)

Rx Only

Each 1 mL contains 16.8 mg of ranitidine hydrochloride. USP equivalent to 15 mg of ranitidine.

Contains 7.5% alcohol.

Usual Dosage: Read prescribing information for Dosage and Administration.

KEEP THIS AND ALL DRUGS OUT OF THE REACH OF CHILDREN.

Store between 4 to 25°C (39 to 77°F).

Do not freeze.

Dispense in a tight, light-resistant container as defined in the USP/NF.

Rx Only

16 fl oz (473 mL)

DO NOT USE IF INNER FOIL SEAL PRINTED "SEALED FOR YOUR PROTECTION" IS BROKEN OR MISSING.
Ranitidine Syrup
(Ranitidine Oral Solution, USP)
Rx Only

DESCRIPTION
The active ingredient in Ranitidine Syrup (Ranitidine Oral Solution, USP) is ranitidine hydrochloride (HCl), USP, a histamine H₂-receptor antagonist. Chemically it is C₁₃H₂₂N₄O₃S·HCl, representing a molecular weight of 350.87.

CLINICAL PHARMACOLOGY
Ranitidine is a competitive, reversible inhibitor of the action of histamine at the histamine H₂-receptors, including receptors on the gastric cells. Ranitidine does not lower serum Ca²⁺ in hypercalcemic states. Ranitidine is not an anticholinergic agent.

Pharmacokinetics:
Absorption: Ranitidine is 50% absorbed after oral administration, compared to an intravenous (IV) injection with mean peak levels of 240 mg to 545 mg/kg, occurring 2 to 3 hours after a 150 mg dose. The oral solution formulation is bioequivalent to the tablets. Absorption is not significantly impaired by the administration of food or antacids. Propranolol 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 antacids (150 mEq) in fasting subjects has been reported to decrease the absorption of ranitidine.

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 amount is < 4% of the dose. Other metabolites are the 5-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 excreted in the urine as unchanged drug (2 in 3 hours). The elimination halflife is about 4.10 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 healthy patients is 48% which is comparable to the bioavailability of ranitidine in the adult population. All other pharmacokinetic parameter values for ranitidine in pediatric patients (from 1 month up to 16 years of age) and adults are similar to those observed with intravenous ranitidine use in pediatric patients.

Pharmacodynamics: Serum concentrations necessary to inhibit 50% of stimulated gastric acid secretion are estimated to be 26 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 inhibits both daytime and nocturnal basal gastric acid secretions as well as gastric acid secretion stimulated by food, histamine, and pentagastrin. The effects of ranitidine on gastric acid secretion are shown in Table 1.

2. Effects on Other Gastrointestinal Secretions:
Phlebitis: Oral ranitidine does not affect peptic ulcer secretion. Total peptic output is reduced in proportion to the decrease in volume of gastric juice.
Intrinsic Factor: Oral ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.
Serum Gastrin: Ranitidine has little or no effect on fasting or postprandial serum gastrin.

Other Pharmacologic Actions:
1. Gastric bacterial flora—Increase in nitrite-reducing organisms, significance not known.
2. Prostaglandin levels—no effect in recommended oral IV dosage, small, transient, dose-related increases in serum prostaglandins have been reported after IV bolus injections of 100 mg or more.
3. Other pituitary hormones—no effect on serum gonadotropins, TSH, or GH.
4. Possible impairment of vasopressin release.
5. No effect on angiotensin.
6. No effect on count, motility, or morphology of sperm.

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

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

Table 3. Duodenal Ulcer Patient Healing Rates

<table>
<thead>
<tr>
<th>Dosage</th>
<th>Patients Healed</th>
<th>% Healed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ranitidine 150 mg</td>
<td>27/68</td>
<td>40%</td>
</tr>
<tr>
<td>Ranitidine 150 mg</td>
<td>24/61</td>
<td>39%</td>
</tr>
</tbody>
</table>

*All patients were permitted antacids as needed for relief of pain.
†P < 0.001 versus placebo.

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

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 (150 mg at bedtime) than in patients treated with placebo over a 12-month period.

Table 5. Duodenal Ulcer Prevalence

<table>
<thead>
<tr>
<th>Maintenance</th>
<th>Ranitidine 150 mg</th>
<th>Placebo*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Patients</td>
<td>12 Months</td>
<td>12 Months</td>
</tr>
<tr>
<td>Ranitidine</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Placebo*</td>
<td>10%</td>
<td>11%</td>
</tr>
</tbody>
</table>

*All patients were permitted antacids as needed for relief of pain.
†P < 0.001 versus 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 Ulcers: In a multicenter, double-blind, controlled, US study of endoscopically diagnosed gastric ulcers, ranitidine became pain free during therapy.

Table 6. Gastric Ulcer Patient Healing Rates

<table>
<thead>
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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 Ulcers: In a multicenter, double-blind, randomized, placebo-controlled, 12-month trials conducted in patients whose gastric ulcers had been previously healed, ranitidine 150 mg at bedtime was significantly more effective than placebo in maintaining healing of erosive esophagitis.

Table 7. Erosive Esophagitis Patient Healing Rates

<table>
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<tr>
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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.

Maintenance of Healing of Erosive Esophagitis: In 2 multicenter, double-blind, randomized, placebo-controlled, 12-week trials performed in the United States, ranitidine 150 mg 4 times daily was significantly more effective than placebo in maintaining healing of erosive esophagitis.

INDICATIONS AND USAGE
Ranitidine Oral Solution is indicated for:
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 4 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 150 mg twice daily.
7. Treatment of erosive denosis for patients with pathological hypersecretory conditions (such as Zollinger-Ellison syndrome) and erosive esophagitis. Placebo-controlled trials have been carried out for 1 year.

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 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 does not preclude the presence of gastric malignancy.
2. Since ranitidine 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 is metabolized in the liver.
3. Rare reports suggest that ranitidine may precipitate acute psychophyric attacks in patients with acute porphyria. Ranitidine 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, primarily due to the presence of sulfonamide and a reactive sulfoxide metabolite.

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 (e.g., those used in the treatment of Zollinger-Ellison syndrome) 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 be prudent to monitor for procarcinamide 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 con-
combinant warfarin and ranitidine therapy. Due to the narrow therapeutic index, close
monitoring of increased or decreased prothrombin time is recommended during concurrent
administration with ranitidine. 

Ranitidine may alter the absorption of drugs in which gastric pH is an important determi-
nant of bioavailability. This can result in either an increase in absorption (e.g., triazolam, midazolam, glipizide) or a decrease in absorption (e.g., ketocazole, atazanavir, delavirdine, gefitinib). Appropriate clinical monitoring is recommended.

**Azatiazine** Azatiazine absorption may be impaired based on known interactions with
other agents that increase gastric pH. Use with caution. See azatiazine label for specific rec-
ommendations.

**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 delava-
dine is not recommended.

**Gefitinib** Gefitinib exposure was reduced by 44% with the coadministration of ranitidine
and sodium bicarbonate (dosed to maintain gastric pH above 5). Use with caution.

**Glipizide** In diabetic patients, glipizide exposure is increased by 34% following a sin-
gle 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 ran-
tidine was coadministered 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
60% when administered with oral ranitidine at a dose of 150 mg twice daily. However, in
another interaction study in 8 volunteers receiving IV midazolam, a 300 mg oral dose of ran-
tidine increased midazolam exposure by about 9%. Monitor patients for excessive or pro-
slurred sedation when ranitidine is coadministered with oral midazolam.

**Trizolm** Trizolm 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 proslurred sedation.

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 2,300 mg/kg/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 dorval test, 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. 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 is administered to a nursing mother.

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

**DOSAGE AND ADMINISTRATION**

**Active Duodenal Ulcer:** The current recommended adult oral dosage of ranti-
dine for duodenal ulcer is 150 mg or 10 mL of oral solution (2 tablets of oral solution equivalent to 150 mg of ranitidine) twice daily. An alternative dosage of 300 mg or 20 mL of oral solution (4 tablets of oral solution equivalent to 300 mg of ran-
tidine) once daily after the evening meal or at bedtime can be used for patients in whom
cessation of healing is important. The advantages of one treatment regimen compared
to the other in a particular patient population have yet to be demonstrated (see Clinical
Trials: Active Duodenal Ulcer). Smaller doses have been shown to be equally effective
in inhibiting gastric acid secretion in US studies, and several foreign trials have shown that
100 mg twice daily is as effective as the 150-mg dose.

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

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

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

**Benign Gastric Ulcer:** The current recommended adult oral dosage is 150 mg or 10 mL of oral solution (2 tablets of oral solution equivalent to 150 mg of ran-
tidine) twice daily.

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

**GERD:** The current recommended adult oral dosage is 150 mg or 10 mL of oral solution (2 tablets of oral solution equivalent to 150 mg of ranitidine) twice daily.

**Erosive Esophagitis:** The current recommended adult oral dosage is 150 mg or 10 mL of oral solution (2 tablets of oral solution equivalent to 150 mg of ranitidine) 4 times daily.

**Maintenance of Healing of Erosive Esophagitis:** The current recommended adult oral dosage is 150 mg or 10 mL of oral solution (2 tablets of oral solution equivalent to 150 mg of ranitidine) twice daily.

**Pediatric Use:** The safety and effectiveness of ranitidine have been established in the age-group of 1 month to 16 years. There is insufficient information about the phar-
macokinetics of ranitidine in neonatal patients (less than 1 month of age) to make

The following 3 subsections provide dosing information for each of the pediatric indica-
tions:

**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/24 hours. This recommendation is derived from adult clinical studies and pharmacokinetic data in pediatric patients.

**Maintenance of Healing of Duodenal and Gastric Ulcers:** The recom-
mended 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/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 func-
tion treated with ranitidine, the recommended dosage in patients with a creatinine
clearance < 50 mL/min is 150 mg or 10 mL of oral solution (2 tablets of oral solution equivalent to 150 mg of ranitidine) every 24 hours. Should the patient's condition require, the frequency of dosing may be increased to every 12 hours or even further with caution. Hemodialysis reduces the level of circulating ranitidine. Ideally, the dosing schedule should be adjusted so that the timing of a scheduled dose coincides with the end of hemodialysis.

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

**HOW SUPPLIED:** Ranitidine Syrup (Ranitidine Oral Solution, USP), a clear to opalescent straw to light-yellow, peppermint-flavored liquid, contains 16.8 mg of ranitidine hydrochloride equivalent to 15 mg of ranitidine per 1 mL (75 mg/mL).

**NDC 70408-141-34 Bottle of 16 fl. oz. (473 mL)** Shown between 4 to 25°C (39 to 77°F).

Do not freeze.

Dispense in a tight, light-resistant container as defined in the USP/NF.

Manufactured by: Nostrum Laboratories, Inc.
Bryan, OH 43006
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