

## **H<sub>2</sub>RA**

Ranitidine (as hydrochloride) 150 mg tablets

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### **Presentation**

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H<sub>2</sub>RA is a white, round tablet marked '150' on one side and '>' on the other side. Each tablet contains 150 mg ranitidine (as hydrochloride).

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### **Uses**

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#### ***Actions***

#### **Pharmacodynamics**

Ranitidine is a selective histamine H<sub>2</sub>-receptor antagonist that competitively inhibits the action of histamine on the H<sub>2</sub>-receptors of the parietal cells. As a result, ranitidine reduces the volume of gastric acid and pepsin secreted under basal conditions, and inhibits gastric acid secretion in response to various stimuli such as histamine, food and pentagastrin. A single 150 mg dose of ranitidine suppresses acid secretion for 12 hours due to its long action duration. Ranitidine has no significant interaction at histamine H<sub>1</sub>-receptors, muscarinic receptors or β-adrenoceptors.

The plasma concentrations of ranitidine achieved are directly related to the doses administered. A plasma ranitidine concentration of 50 to 100 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%.

Inhibition of pentagastrin-induced gastric acid secretion increases with dose, being approximately 90% two hours after an oral 150 mg dose and a significant effect is still evident 12 hours after this dose. In 10 patients with duodenal ulcer, ranitidine 150 mg given orally every 12 hours significantly reduced the mean 24-hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90%, whereas cimetidine (200 mg three times daily and 400 mg at night) reduced the mean 24-hour hydrogen ion activity by 48% and nocturnal gastric acid output by 70%.

Pepsin secretion is also inhibited by ranitidine, 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.

Reduction in gastric acid secretion induced by ranitidine 150 mg twice daily for seven days did not cause bacterial overgrowth in the stomach.

Pulse rate, blood pressure, ECG and EEG were not significantly affected in humans following recommended doses of ranitidine.

Chronic ranitidine therapy (300 mg/day for 28 days) had no effect on serum prolactin, gastrin, thyroid stimulating hormone, follicle stimulating hormone, luteinising hormone, gonadotrophins, testosterone, oestriol, progesterone or cortisol levels.

One study in 30 male patients with duodenal ulcer showed a significant decrease in basal thyroxine levels after 4 weeks of treatment with ranitidine 300 mg daily, but no significant change in thyroid stimulating hormone was noted. Acute administration of ranitidine 50 mg intravenously had no effect on plasma aldosterone in healthy male volunteers whereas it caused a significant reduction in vasopressin. Cimetidine 200 mg intravenously had a similar effect on vasopressin.

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## Pharmacokinetics

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### ***Absorption***

After oral administration, ranitidine is rapidly absorbed and peak plasma concentrations occur within 2 to 3 hours. Absorption is not significantly altered by food or concurrent antacid administration (e.g. 10 mL). However, absorption may be decreased by large doses of antacids.

### ***Distribution***

Bioavailability of ranitidine is approximately 50% due to first-pass metabolism. This may increase to 70% in people with hepatic cirrhosis. Ranitidine is widely distributed and the serum protein binding of in humans is in the range 10 to 19%. The average apparent volume of distribution in adults is 1.9 L/kg, and in children (3.5 to 16 years old) is approximately 2.4 L/kg.

### ***Metabolism***

Ranitidine is partially metabolised in the liver to form N-oxide, S-oxide, desmethyranitidine and the furoic acid analogue.

### ***Elimination***

Ranitidine is excreted principally in the urine, via glomerular filtration and tubular secretion, as unchanged drug and in minor amounts of the metabolites. The elimination half-life of ranitidine is about 2.5 hours and renal clearance is 410 to 512 mL/minute. The 24-hour urinary recovery of free ranitidine and its metabolites is about 40% after a single 150 mg dose. The remainder of the absorbed dose is eliminated in faeces, via biliary excretion.

### ***Special patient groups***

In patients with renal impairment, the elimination half-life is prolonged and dosage reduction would be necessary (see **Warnings and Precautions**). Ranitidine is removed by haemodialysis.

Impairment of liver function may increase the bioavailability of ranitidine but has no significant effect on the elimination half-life. In the presence of normal renal function, no dosage reduction for ranitidine appears necessary in patients with hepatic impairment.

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## Indications

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H<sub>2</sub>RA is indicated for the symptomatic relief of heartburn, dyspepsia and hyperacidity, which can be associated with reflux oesophagitis, functional dyspepsia and/or peptic ulcers.

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## Dosage and Administration

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### Adults and children over 12 years of age

The recommended dose is one H<sub>2</sub>RA tablet. The tablet should be swallowed with water, with or without food. It is recommended to start the treatment at the first sign of heartburn or reflux.

If symptoms recur, a second tablet may be taken 1 hour later if needed. Do not take more than two tablets in 24 hours.

H<sub>2</sub>RA tablets should not be taken for more than 14 days without seeking medical advice.

### Children under 12 years of age

H<sub>2</sub>RA is not recommended for use in children under 12 years of age, as its safety and efficacy has not been fully studied in this group.

### Renal impairment

For patients with a creatinine clearance (Cl<sub>Cr</sub>) less than 50 mL/minute, the daily dose of H<sub>2</sub>RA should not exceed 150 mg. For those with Cl<sub>Cr</sub> less than 10 mL/minute, H<sub>2</sub>RA should either be avoided or no more than 150 mg on alternate days.

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## Contraindications

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Patients with known hypersensitivity to ranitidine hydrochloride or to any component of the product (see **Further Information**).

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## Warnings and Precautions

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Patients should seek medical advice for the following conditions before commencing or continuing the ranitidine therapy:

- worsening indigestion and/or heartburn symptoms, new or additional symptoms, or recurrent symptoms
- indigestion symptoms occur for the first time at age over 40 years old
- unintended weight loss, vomiting, haematemesis, diarrhoea or melaena
- concurrent treatment with non-steroidal anti-inflammatory drugs
- history of peptic ulcers.

### Gastric ulcer

Treatment with a histamine H<sub>2</sub>-antagonist may mask symptoms associated with carcinoma of the stomach and thus delay diagnosis of the condition. The possibility of malignancy should be excluded before commencement of therapy especially in

patients with gastric ulcer, or in middle-aged or older patients with new or changed dyspeptic symptoms.

### **Porphyria**

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

### **Community acquired pneumonia**

In elderly patients, patients with chronic lung disease, diabetes or the immunocompromised, there may be an increased risk of developing community acquired pneumonia. A large epidemiological study showed an increased risk of developing community acquired pneumonia in current users of H<sub>2</sub>-receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1.63.

### **Renal impairment**

Ranitidine is excreted via the kidneys, and in the presence of severe renal impairment, plasma levels of ranitidine are increased and prolonged. The dosage should be adjusted accordingly (see **Dosage and Administration**). The clearance of ranitidine is increased during haemodialysis.

### **Smoking**

Smoking can be associated with a higher rate of duodenal ulcer relapse, and thus the recurrence of heartburn and/or indigestion symptoms.

### **Use in children**

Experience with ranitidine tablets in children is limited and such use has not been fully evaluated in clinical studies. While ranitidine has been used successfully in children aged 8 to 18 years in doses up to 150 mg twice daily, H<sub>2</sub>RA tablets are not recommended in children under 12 years of age.

### **Use in pregnancy (Category B1)**

Ranitidine crosses the placenta. Therapeutic doses administered to women in labour have been without adverse effect on labour, delivery or neonatal outcome. However, there have been no well controlled studies of use in pregnant women. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or teratogenicity. However, these studies are not always predictive of response in humans. Ranitidine should only be used in pregnancy where there is a clearly identified need.

### **Use in lactation**

Ranitidine crosses into breast milk and multiple dosing results in higher concentrations in breast milk than in serum, especially towards the end of a 12-hour dosing interval. Minimum milk concentration occurs 1 to 2 hours after maternal administration. Nursing is best avoided if possible.

### **Effects on ability to drive or operate machinery**

Ranitidine rarely causes dizziness and is unlikely to affect the ability to drive or operate machinery. However, individual response should be determined before driving or performing tasks requiring alertness.

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## **Adverse Effects**

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The following have been reported as events in clinical trials or in the routine management of patients treated with ranitidine. The relationship to ranitidine therapy has not been clear in many cases.

### **Central nervous system**

Headache, sometimes severe, has been reported in a very small proportion of patients. Rarely, malaise, dizziness, somnolence, insomnia and vertigo occur. Rare cases of reversible mental confusion, depression and hallucinations have been reported, predominantly in severely ill and elderly patients. In addition, reversible involuntary movement disorders have been reported rarely. Reversible impotence has been reported rarely.

### **Optic disorders**

There have been a few reports of reversible blurred vision suggestive of a change in accommodation.

### **Cardiovascular system**

As with other H<sub>2</sub>-receptor antagonists, there have been rare reports of tachycardia, bradycardia, premature ventricular beats, atrioventricular block and asystole. Rare cases of vasculitis have been reported.

### **Gastrointestinal system**

Constipation, diarrhoea, nausea, vomiting, abdominal discomfort or pain can occur.

### **Hepatobiliary tract and pancreas**

Transient and reversible changes in liver function tests can occur. There have been occasional reports of hepatitis (hepatocellular, hepatocanalicular or mixed), with or without jaundice. These were usually reversible. Acute pancreatitis has been rarely reported.

### **Renal disorders**

Small increases in serum creatinine may occur. Very rare cases of acute interstitial nephritis have been reported.

### **Blood and lymphatic system**

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

### **Musculoskeletal disorders**

Arthralgia and myalgia have been reported rarely.

### **Endocrine system**

Controlled studies in animals and humans have shown no stimulation of any pituitary hormone by ranitidine, no anti-androgenic activity, and cimetidine-induced gynaecomastia and impotence in hypersecretory patients have resolved when ranitidine was substituted. However, occasional cases of gynaecomastia, impotence and loss of libido have been reported in male patients receiving ranitidine, but the incidence did not differ from that in the general population.

### **Dermatological disorders**

Skin rash has been reported, including rare cases of erythema multiforme. Rarely, alopecia can occur.

### **Others**

Hypersensitivity reactions (urticaria, angioneurotic oedema, fever, bronchospasm, hypotension, anaphylactic shock, chest pain) have been seen rarely after a single dose.

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## **Interactions**

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Ranitidine, at blood levels produced by standard recommended doses, does not inhibit the hepatic cytochrome P450-linked mixed function oxygenase system. In usual therapeutic doses, ranitidine does not potentiate the actions of drugs that are inactivated by this enzyme. These drugs include diazepam, lignocaine, phenytoin, propranolol, theophylline and warfarin. There is no evidence of an interaction between ranitidine and amoxicillin and metronidazole.

If high doses (2 g) of sucralfate are co-administered with ranitidine, the absorption of the latter may be reduced. This effect is not seen if sucralfate is taken after an interval of 2 hours.

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## **Overdosage**

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There has been limited experience with overdoses of ranitidine tablets. Reported acute ingestions of up to 18 g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (see **Adverse Effects**). Symptomatic and supportive therapy should be given as appropriate. If needed, the drug may be removed from the plasma by haemodialysis.

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## **Pharmaceutical Precautions**

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### **Shelf Life**

36 months

### **Storage**

Store in a cool, dry place where it stays below 25°C

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## Medicine Classification

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Pharmacy Only Medicine

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## Package Quantities

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Blister pack of 10 tablets

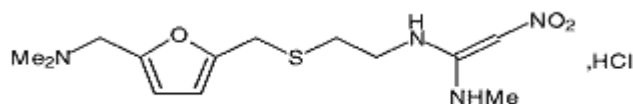
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## Further Information

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H<sub>2</sub>RA contains the hydrochloride salt of ranitidine.

The chemical name for ranitidine hydrochloride is N-(2-(((5-((dimethylamino)methyl)-2-furanyl)methyl)thio)ethyl)-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride. Its structural formula is:



C<sub>13</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>S.HCl

Molecular weight: 350.9

CAS: 66357-59-3

Ranitidine hydrochloride is a white or pale yellow crystalline powder with a slightly bitter taste and sulfur-like odour. It is an aminoalkyl substituted furan and is structurally different from cimetidine, lacking the imidazole ring and the cyanoguanidine group. Ranitidine hydrochloride is freely soluble in water and methanol and sparingly soluble in ethanol (96%).

H<sub>2</sub>RA tablets also contain the following excipients: microcrystalline cellulose, croscarmellose sodium, magnesium stearate and Opadry II White YS-22-18096. The tablets are gluten free.

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## Name and Address

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## Date of Preparation

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