AUSTRALIAN PRODUCT INFORMATION

RANI 2

Ranitidine hydrochloride

Mylan

1 NAME OF THE MEDICINE

Ranitidine hydrochloride

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each Rani 2 tablet contains ranitidine hydrochloride as the active ingredient equivalent to 150 mg or 300 mg of ranitidine. For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Rani 2 150 mg: Creamish yellow, biconvex, round, film-coated tablets with ”G” on one side and “00” over “30” on the reverse.

Rani 2 300 mg: Creamish yellow, biconvex, capsule shaped, film-coated tablets with “G” on one side and “0031” on the reverse.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Short-term treatment of proven duodenal ulcer and gastric ulcer.

Maintenance treatment to reduce the risk of relapse in duodenal ulcer.

Maintenance treatment for periods up to one year to reduce the risk of relapse in patients with documented healing of benign gastric ulcer.

Treatment of gastrinoma (Zollinger-Ellison syndrome).

Short-term symptomatic treatment of reflux oesophagitis unresponsive to conservative anti-reflux measures and simple drug therapies such as antacids.

Maintenance treatment to reduce the risk of relapse of reflux oesophagitis.

Treatment of scleroderma oesophagitis.

4.2 DOSE AND METHOD OF ADMINISTRATION

Acute duodenal or gastric ulceration

Acute treatment

300 mg taken as a single dose at bedtime, or 150 mg taken twice daily, in the morning and at bedtime.

It is not necessary to time the dose in relation to meals. In most cases healing will occur in four weeks although a small number of patients may require an additional two to four weeks therapy.

Maintenance treatment of duodenal ulcer

150 mg taken at night. As smoking is associated with a higher rate of ulcer relapse, patients should be advised to stop smoking. In patients unable to stop smoking, a dose of 300 mg at night provides additional therapeutic benefit.

Maintenance treatment of gastric ulcer

150 mg taken at night for a period of one year.

Gastrinoma (Zollinger-Ellison syndrome)

150 mg taken three times daily initially and increased, as necessary, to 600 to 900 mg/day.

Reflux oesophagitis

Symptomatic treatment of reflux oesophagitis

300 mg taken as a single dose at bedtime or 150 mg taken twice daily in the morning and at bedtime. It is not necessary to time the dose in relation to meals.

In severe reflux oesophagitis the efficacy of 300 mg, taken as a single dose at bedtime, has been established for up to three months.

Maintenance treatment of reflux oesophagitis

150 mg taken twice daily in the morning and at bedtime.

4.3 CONTRAINDICATIONS

Patients with known hypersensitivity to ranitidine hydrochloride or any components of Rani 2 tablets.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Gastric ulcer

Treatment with a histamine H2-antagonist may mask symptoms associated with carcinoma of the stomach and therefore may delay diagnosis of the condition. Accordingly, where gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with ranitidine is instituted.

Long-term Use

The risk of ulcer recurrence is determined by many factors. In some cases, long periods of treatment may be necessary and/or repeated. Evidence from controlled clinical trials of up to 18 months continuous treatment with ranitidine has not revealed any undue untoward effects.

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.

Gastric pH

Agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia in intubated intensive care patients receiving mechanical ventilation.

Pneumonia

In patients such as the elderly, persons 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 H2-receptor antagonists versus those that had stopped treatment, with an observed adjusted relative risk of 1.63 (95% Cl, 1.07-2.48).

Use in Renal Impairment

Ranitidine is excreted via the kidneys and in the presence of renal impairment plasma levels of ranitidine are increased and prolonged. Accordingly in the presence of significant renal impairment, serum levels should be monitored and dosage adjustments made. The clearance of ranitidine is increased during haemodialysis.

Use in the Elderly

No data available.

Paediatric Use

Experience with ranitidine tablets in children is limited and such use has not been fully evaluated in clinical studies. It has however, been used successfully in children aged 8 to 18 years in doses up to 150 mg twice daily.

Effects on Laboratory Tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Ranitidine has the potential to affect the absorption, metabolism or renal excretion of other drugs. The altered pharmacokinetics may necessitate dosage adjustment of the affected drug or discontinuation of treatment.

Interactions occur by several mechanisms including:

1. Inhibition of cytochrome P450-linked mixed function oxygenase system:

   Ranitidine at usual therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme system such as diazepam, lidocaine, phenytoin, propranolol and theophylline.

   There have been reports of altered prothrombin time with coumarin anticoagulants (e.g. warfarin). Due to the narrow therapeutic index, close monitoring of increased or decreased prothrombin time is recommended during concurrent treatment with ranitidine.

2. Competition for renal tubular secretion:

   Since ranitidine is partially eliminated by the cationic system, it may affect the clearance of other drugs eliminated by this route. High doses of ranitidine (e.g. such as those used in the treatment of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

3. Alteration of gastric pH:

   The bioavailability of certain drugs may be affected. This can result in either an increase in absorption (e.g. triazolam, midazolam, glipizide) or a decrease in absorption (e.g. ketoconazole, atazanavir, delaviridine, gefitinib).

   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 two hours.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

There are no data on the effects of ranitidine on human fertility. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine.

Use in Pregnancy

Pregnancy Category: B1

The safety of ranitidine in pregnancy has not been established. Ranitidine crosses the placenta and should only be used during pregnancy if considered essential. 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 foetus.

Use in Lactation

Ranitidine is secreted in breast milk in lactating mothers, but the clinical significance of this has not been fully evaluated. Ranitidine should only be used by breastfeeding mothers if considered essential.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed as part of its registration.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

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. Headache, sometimes severe, has been reported in a very small proportion of patients.

Central Nervous System

Rarely, malaise, dizziness, somnolence, insomnia and vertigo. 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. There have been a few reports of reversible blurred vision suggestive of a change in accommodation. Reversible impotence has been reported rarely.

Cardiovascular

As with other H2-receptor antagonists rare reports of tachycardia, bradycardia, premature ventricular beats, atrioventricular block, and asystole.

Gastrointestinal

Constipation, diarrhoea, nausea/vomiting, abdominal discomfort/pain.

Musculoskeletal

Rare reports of arthralgias and myalgia.

Haematologic

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

Endocrine

Controlled studies in animals and man 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 breast conditions such as gynaecomastia and galactorrhoea, 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.

Integumental

Rash including rare cases of mild erythema multiforme. Rare cases of vasculitis and alopecia have been reported.

Hepatic

Transient and reversible changes in the liver function tests can occur. In normal volunteers, SGPT values were increased to at least twice the pre-treatment levels in 6 of 12 subjects receiving 100 mg intravenously four times daily for 7 days, and in 4 of 24 subjects receiving 50 mg intravenously four times daily for 5 days. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

Renal

Very rare cases of acute interstitial nephritis have been reported.

Other

Rare cases of hypersensitivity reactions (e.g. fever, bronchospasm, anaphylactic shock, urticaria, angioneurotic oedema, rash, eosinophilia, chest pain, hypotension), small increases in serum creatinine. Acute pancreatitis has been reported rarely.

Reporting Suspected Adverse Effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Symptoms

There has been limited experience with oral doses of ranitidine. Reported acute ingestions of up to 18g orally have been associated with transient adverse effects similar to those encountered in normal clinical experience (See Section 4.8 Adverse Effects (Undesirable Effects)).

Treatment

Clinical monitoring, symptomatic and supportive therapy should be employed.

If need be, the drug may be removed from the plasma by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of Action

Ranitidine hydrochloride is a histamine H2-receptor antagonist.

Animal experiments both in vitro and in vivo have established that ranitidine is a selective, competitive antagonist of histamine at H2-receptor sites. Ranitidine has no significant interaction at histamine H1-receptors, muscarinic receptors or beta-adrenoceptors. Ranitidine is a potent inhibitor of gastric secretion in the rat and dog.

Clinical Trials

All the evidence from human studies is compatible with a selective, competitive antagonism of histamine H2-receptors by ranitidine in man. Oral or intravenous administration of ranitidine inhibits both basal gastric secretions and gastric acid secretion induced by histamine, pentagastrin and other secretagogues. On a weight basis ranitidine is between four and nine times more potent than cimetidine.

After oral administration of ranitidine, the plasma concentrations of ranitidine achieved are directly related to the dose administered. A plasma ranitidine concentration of 50 to 100 nanogram/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, 150 mg ranitidine given orally every 12 hours significantly reduced 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 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, electrocardiogram and electroencephalogram were not significantly affected in man 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, estriol, progesterone or cortisol levels.

One study in 30 male duodenal ulcer patients showed a significant decrease in basal thyroxine levels after 4 weeks treatment with 300 mg ranitidine daily, but no significant change in thyroid stimulating hormone was noted. Acute administration of 50 mg ranitidine 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.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Peak plasma levels occur about two to three hours after oral administration of ranitidine. Absorption is not significantly altered by food or concurrent antacid administration.

Following oral administration of 150 mg ranitidine, maximum plasma concentrations (300 to 580 ng/mL) occurred after 1 to 3 hours. Two distinct peaks or a plateau in the absorption phase suggest reabsorption of drug secreted into the intestine. The absolute bioavailability of ranitidine is 50 to 60%, and plasma concentrations increase proportionally with increasing dose up to 200 mg. Bioavailability of ranitidine is approximately 50%. Serum protein binding of ranitidine in man is in the range 10% to 19%. The elimination half-life is approximately two hours.

Distribution

Ranitidine is not extensively bound to plasma proteins (15%), but exhibits a large volume of distribution ranging from 96 to 142 L.

Metabolism

The fraction of the dose recovered as metabolites is similar after both oral and intravenous dosing and includes 6% of the dose in urine as the N-oxide, 2% as the S-oxide and small amounts of desmethylranitidine and the furoic acid analogue.

The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% after oral administration of the drug.

Excretion

Plasma concentrations decline bi-exponentially, with a terminal half-life of 2 to 3 hours. The major route of elimination of unchanged ranitidine is renal. Renal clearance is approximately 500 mL/min, which exceeds glomerular filtration indicating net renal tubular secretion.

Patients over 50 years of age

In patients over 50 years of age, half-life is prolonged (3 to 4 hours) and clearance is reduced, consistent with the age-related decline of renal function. However, systemic exposure and accumulation are 50% higher. This difference exceeds the effect of declining renal function, and indicates increased bioavailability in older patients.

Impairment of renal function requires a reduction in dosage (see Section 4.4 Special Warnings and Precautions for Use). Impairment of liver function may increase the bioavailability of ranitidine but has no significant effect on the elimination half-life. However, in the presence of normal renal function, no dosage reduction for oral ranitidine appears necessary in patients with hepatic impairment.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No data available.

Carcinogenicity

No data available.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain the following inactive excipients: microcrystalline cellulose, magnesium stearate, hypromellose, castor oil, iron oxide yellow, titanium dioxide and purified talc. The 300 mg tablets also contain croscarmellose sodium.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Bottles (HDPE) – Store below 25°C.

Blister packs (Al/Al) – Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Rani 2 150 mg: Ranitidine hydrochloride 150 mg, bottles and blister packs of 60 tablets.

Rani 2 300 mg: Ranitidine hydrochloride 300 mg bottles and blister packs of 30 tablets.

Some strengths, pack sizes and/or pack types may not be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

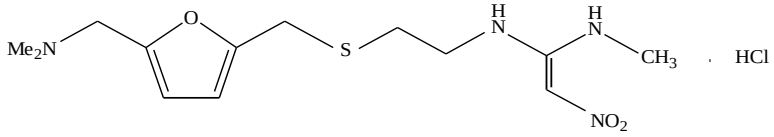
In Australia, any unused medicine or waste material should be disposed of by taking it to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ranitidine hydrochloride is a white or pale yellow, crystalline powder, freely soluble in water and in methanol, sparingly soluble in ethanol, very slightly soluble in methylene chloride.

Ranitidine is an aminoalkyl-substituted furan and is structurally different from cimetidine lacking the imidazole ring and the cyanoguanidine group.

Chemical Structure



Chemical name: N-(2-(((5-((dimethylamino)methyl)-2-furan-yl)methyl)thio)ethyl)-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride.

Molecular formula: $C_{13}H_{22}N_4O_3S.HCl$

Molecular weight: 350.9

CAS Number

66357-59-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 (Prescription Only Medicine)

8 SPONSOR

Alphapharm Pty Ltd

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

www.mylan.com.au

9 DATE OF FIRST APPROVAL

28/06/2002

10 DATE OF REVISION

26/02/2020

Summary Table of Changes

Section Changed	Summary of New Information
All	Updated to align with the new PI format.
4.1	Minor editorial changes.
5.1	Minor editorial changes to align with IHIN.
6.5, 8	Section updated.

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