

# NEW ZEALAND DATA SHEET

## RANITIDINE RELIEF



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### 1. Product Name

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Ranitidine Relief, 150 mg, 300 mg, film coated tablet.

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### 2. Qualitative and Quantitative Composition

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Each film coated tablet contains 150 mg or 300 mg of ranitidine (as hydrochloride).

For the full list of excipients, see section 6.1.

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### 3. Pharmaceutical Form

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Ranitidine Relief 150mg tablet: a creamy-yellow, round, biconvex film coated tablet marked R150 on one side.

Ranitidine Relief 300mg tablet: a creamy-yellow, round, biconvex film coated tablet marked R300 on one side.

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### 4. Clinical Particulars

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#### 4.1 Therapeutic indications

Ranitidine Relief is indicated for the treatment of duodenal ulcer and benign gastric ulcer.

The pathogenesis of duodenal ulcer disease is multifactorial and infection with *Helicobacter pylori* appears to be one important factor in the process. The United States National Institute of Health has recommended that regimens to eradicate *Helicobacter pylori* in patients with peptic ulcer disease, whether on first presentation with the illness or on recurrence, should contain both anti-secretory agents (including H<sub>2</sub>-antagonists) and anti-microbial agents (to which *Helicobacter pylori* has been demonstrated to be sensitive *in vivo*). A trial in patients with recurrent duodenal ulcer disease demonstrated that ranitidine in combination with amoxicillin (750 mg three times daily) and metronidazole (500 mg three times daily) for 12 days is effective in eradicating *Helicobacter pylori* in 89% of cases. Following this combination therapy the relapse rate for duodenal ulcer disease was only 2% at 12 months suggesting a causal role for *Helicobacter pylori* in recurrent duodenal ulcer. Therefore ranitidine, when used in a treatment regimen with amoxicillin and metronidazole, is indicated for the treatment of duodenal ulcers associated with *Helicobacter pylori* infection.

Ranitidine Relief is also indicated for:

- the treatment of duodenal ulcer and benign gastric ulcer associated with non-steroidal anti-inflammatory agents.
- the prevention of non-steroidal anti-inflammatory agent (including aspirin) associated duodenal ulcers in patients with a history of duodenal ulceration proven by endoscopy.
- the treatment of post-operative ulcer

- the treatment of chronic episodic dyspepsia, characterised by pain (epigastric or retrosternal) which is related to meals or disturbs sleep but not associated with the above conditions.
- symptom relief in gastro-oesophageal reflux disease
- the treatment of oesophageal reflux disease
- the treatment of Zollinger-Ellison syndrome

Ranitidine Relief is also indicated for the following conditions where reduction of gastric secretion and acid output is desirable:

- the prophylaxis of upper gastrointestinal haemorrhage from stress ulceration in seriously ill patients.
- the prophylaxis of recurrent haemorrhage in patients with bleeding peptic ulcers.
- before general anaesthesia in patients considered to be at risk of acid aspiration (Mendelson's syndrome), particularly obstetric patients during labour.

### **Pharmacy-Only and General Sale indication**

Ranitidine Relief is indicated for the symptomatic relief of heartburn, dyspepsia and hyperacidity in adults and children over 12 years.

## **4.2 Dose and method of administration**

### **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: 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.

### **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.

### **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 treatment periods of up to three months.

Maintenance treatment for reflux oesophagitis. 150 mg taken twice daily in the morning and at bedtime.

### **Acute symptomatic relief of heartburn, dyspepsia and hyperacidity**

Take one 300 mg tablet at the first sign of any symptoms. Do not exceed one tablet in 24 hours.

Or

Take one 150 mg tablet at the first sign of any symptoms. Repeat the dose if the symptoms return. Do not exceed two tablets in 24 hours.

### **4.3 Contraindications**

Patients with known hypersensitivity to ranitidine hydrochloride or to any component of this product listed in section 6.1

### **4.4 Special warnings and precautions for use**

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 increase 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 (95% CI, 1.07- 2.48).

Use with caution in the following circumstances:

#### **Gastric ulcer**

Treatment with a histamine H<sub>2</sub>-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 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 ICU patients receiving mechanical ventilation.

#### **Impaired renal function**

Ranitidine is excreted via the kidneys and in the presence of severe 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 children**

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.

### **4.5 Interaction with other medicines and other forms of interaction**

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:

## **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.

## **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.

## **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, delavirdine, 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**

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

The safety of ranitidine in pregnancy has not been established. Ranitidine crosses the placenta. Ranitidine 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 nursing mothers if considered essential.

### **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.

## **4.7 Effects on ability to drive and use machines**

Not relevant.

## **4.8 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 H<sub>2</sub>-receptor antagonists, rare reports of tachycardia, bradycardia, premature ventricular beats, A-V block and asystole.

## **Gastrointestinal**

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

## **Musculoskeletal**

Rare reports of arthralgias and myalgia.

## **Haematological**

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 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 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.

## **Dermatological**

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

## **Renal**

Very rare cases of acute interstitial nephritis have been reported.

## **Hepatic**

Transient and reversible changes in liver-function tests can occur. There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible.

## **Other**

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

## **Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

## **4.9 Overdose**

### **Symptoms**

There has been limited experience of overdosage with oral doses of ranitidine. 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 section 4.8).

## Treatment

Symptomatic and supportive therapy should be given as appropriate. If need be, the drug may be removed from the plasma by haemodialysis.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

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## 5. Pharmacological Properties

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### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: H<sub>2</sub>-receptor antagonists, ATC code: A02BA02

#### Pharmacology

Animal experiments both *in vitro* and *in vivo* have established that ranitidine is a selective, competitive antagonist of histamine at H<sub>2</sub>-receptor sites. Ranitidine has no significant interaction at histamine H<sub>1</sub>-receptors, muscarinic receptors or beta-adrenoreceptors. Ranitidine is a potent inhibitor of gastric secretion in the rat and dog.

All the evidence from human studies is compatible with a selective, competitive antagonism of histamine H<sub>2</sub>-receptors by ranitidine in humans. Oral 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 ten patients with duodenal ulcer, ranitidine 150 mg 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, 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 four weeks of treatment with ranitidine 300 mg daily, but no significant change in thyroid stimulating hormone was noted.

## **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.

Bioavailability of ranitidine is approximately 50%. Serum protein binding of ranitidine in humans is in the range of 10 to 19%. The elimination half-life is approximately two hours.

### **Metabolism**

The fraction of the dose recovered as metabolites after oral dosing 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.

### **Pharmacokinetic/pharmacodynamic relationship(s)**

#### ***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). Impairment of hepatic 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 ranitidine appears necessary in patients with hepatic impairment.

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## **6. Pharmaceutical Particulars**

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### **6.1 List of excipients**

Ranitidine Relief tablets also contain the following excipients:

- magnesium stearate,
- microcrystalline cellulose,
- colloidal anhydrous silica,
- croscarmellose sodium,
- purified talc,
- isopropyl alcohol,
- yellow iron oxide,
- titanium dioxide, castor oil
- hypromellose.

The tablets are gluten and lactose free.

### **6.2 Incompatibilities**

Not applicable.

### **6.3 Shelf life**

2 years.

### **6.4 Special precautions for storage**

Store at or below 25°C.

## **6.5 Nature and contents of container**

Ranitidine Relief 150mg are available in Al/Al blister packs of 10, 20, 28, 250 or 500 tablets.

Ranitidine Relief 300mg are available in Al/Al blister packs of 10, 14, 250 or 500 tablets.

Not all pack types and sizes may be marketed.

## **6.6 Special precautions for disposal**

Not applicable.

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## **7. Medicines Schedule**

General Sale Medicine: 150 mg blister pack of 10 tablets

Pharmacy Only Medicine: 150 mg blister pack of 20 or 28 tablets and 300 mg blister pack of 10 or 14 tablets

Prescription Only Medicine: 150mg and 300 mg blister pack of 250 and 500 tablets

Not all strengths and pack sizes may be marketed

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## **8. Sponsor Details**

Mylan New Zealand Ltd  
PO Box 11183  
Ellerslie  
AUCKLAND  
Telephone 09-579-2792

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## **9. Date of First Approval**

General Sale Medicine: 150 mg: 02 July 2015

Pharmacy Only Medicine: 150 mg and 300 mg: 18 February 2010

Prescription Only Medicine: 150mg and 300 mg: 20 September 2012

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## **10. Date of Revision of the Text**

14 August 2018

Section	Summary of changes
-	Revised to SmPC format
5.1	Removal of IV information
5.2	Update to absorption, removal of distribution and excretion to align with source data sheet