

# NEW ZEALAND DATASHEET

## Ranihexal

*Ranitidine hydrochloride, film coated tablets, 150 mg and 300 mg (as ranitidine)*

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### Presentation

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#### 150 mg

Yellow, 9 mm round, film coated tablets, scored on one side. Each tablet contains ranitidine hydrochloride equivalent to ranitidine 150 mg.

#### 300 mg

Yellow, 17 mm x 7 mm oblong, film-coated tablets, scored on one side. Each tablet contains ranitidine hydrochloride equivalent to ranitidine 300 mg.

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### Uses

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#### Actions

Ranitidine hydrochloride is a histamine H<sub>2</sub>-receptor antagonist. It is an aminoalkyl-substituted furan and is structurally different from cimetidine, lacking the imidazole ring and cyanoguanidine moieties.

#### Pharmacotherapeutic group

A02BA02 - H<sub>2</sub>-receptor antagonists, ranitidine.

#### Mechanism of action

Ranitidine is a specific, rapidly acting histamine H<sub>2</sub>-receptor antagonist. It inhibits basal and stimulated secretion of gastric acid, reducing both the volume and the acid and pepsin content of the secretion.

#### Pharmacodynamic effects

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%.

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 daily 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 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.

### **Onset and duration of action**

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%.

## ***Pharmacokinetics***

### **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%.

### **Distribution**

Serum protein binding of ranitidine in humans is in the range of 10 to 19%.

### **Biotransformation**

Ranitidine is not extensively metabolised. Ranitidine is excreted via the kidneys mainly as unchanged drug and in minor amounts as the N-oxide, S-oxide and desmethyl metabolites. In mass balance studies with 150 mg <sup>3</sup>H labelled ranitidine, 60 to 70% of an oral dose was excreted in urine and 26% in faeces. Analysis of urine excreted in the first 24 hours after dosing showed that 70% of the intravenous dose and 35% of the oral dose were eliminated unchanged. The metabolism of ranitidine is similar after both oral and intravenous dosing; about 6% of the dose being excreted in urine as the N-oxide, 2% as the S-oxide, 2% as desmethylranitidine and 1 to 2% as the furoic acid analogue.

### **Elimination**

Elimination of the drug is primarily by tubular secretion. The elimination half life is approximately two hours.

### **Special patient considerations**

Impairment of renal function requires a reduction in dosage. 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 intravenous ranitidine appears necessary in patients with hepatic impairment.

## ***Indications***

### **Treatment of duodenal ulcer and benign gastric ulcer**

Infection with *Helicobacter pylori* is recognised as an important factor in the pathophysiology of peptic ulcer disease. Accordingly, eradication of the infection is the single most important therapeutic intervention for patients with a positive diagnosis of *Helicobacter pylori* infection.

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>-receptor antagonists) and anti-microbial agents (to which *Helicobacter pylori* has been demonstrated to be sensitive *in vivo*). A study by Hentschel E, Brandstätter G, Dragosics B *et al.* (N Engl J Med 1993; 328: 308-312) in patients with recurrent duodenal ulcer disease has 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 amoxycillin and metronidazole, is indicated for the treatment of duodenal ulcers associated with *Helicobacter pylori* infection.

### **Other indications**

Treatment of duodenal ulcer and benign gastric ulcer associated with non-steroidal anti-inflammatory agents.

Prevention of non-steroidal anti-inflammatory agent (including aspirin) associated duodenal ulcers in patients with a history of duodenal ulceration proven by endoscopy.

Treatment of post-operative ulcer

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

Treatment of oesophageal reflux disease

Treatment of Zollinger-Ellison syndrome

The following conditions where reduction of gastric secretion and acid output is desirable: prophylaxis of upper gastrointestinal haemorrhage from stress ulceration in seriously ill patients; 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.

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## **Dosage and administration**

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### **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.

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## **Contraindications**

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Known hypersensitivity to ranitidine or to any of the inactive ingredients listed in [Further information](#).

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## **Warnings and precautions**

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### **Warnings**

#### **Community acquired 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 H<sub>2</sub>-receptor antagonists against those who had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07-2.48).

#### **Gastric ulcer**

Treatment with a histamine H<sub>2</sub>-receptor 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 ranitidine therapy is instituted.

### **Precautions**

#### **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 of 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 unit 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 preparations in children is limited and such use has not been fully evaluated in clinical studies. Ranitidine has, however, been used successfully in children aged 8 to 18 years in doses up to 150 mg twice daily.

### **Lactose intolerance**

Since this medicinal product contains lactose, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### ***Pregnancy and lactation***

#### **Use in pregnancy**

Assigned Category B1 by the Australian Drug Evaluation Committee. This category includes medicines which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have not shown evidence of an increased occurrence of foetal damage.

The safety of ranitidine in pregnancy has not been established. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine. 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**

Residual ranitidine may be present in breast milk at levels corresponding to 5.0 to 7.8% of the maternal dose. Ranitidine is probably safe when restricted to sporadic doses or a single dose at night-time, however it may accumulate in milk due to active transport.

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

This medicine is presumed to be safe or unlikely to produce an effect.

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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 and dizziness have been reported in a very small proportion of patients. 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.

#### **Cardiovascular**

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

#### **Gastrointestinal**

Constipation, nausea/vomiting, abdominal discomfort/pain, and very rarely, diarrhoea.

#### **Hepatic**

Transient and reversible changes in liver function tests can occur. In normal volunteers, ALT 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 milligrams 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.

#### **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 gynaecomastia, reversible 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 alopecia have been reported.

### **Renal**

Very rare cases of acute interstitial nephritis have been reported.

### **Special senses**

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

### **Other**

Hypersensitivity reactions manifested by skin rash, urticaria, chest pain, hypotension, fever, eosinophilia, bronchospasm, angioneurotic oedema, and anaphylactic shock have been observed rarely after a single dose.

Small increases in serum creatinine have occurred rarely. Acute pancreatitis has been reported rarely.

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## **Interactions**

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### ***Medicines and other pharmacologically active substances***

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.

#### **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 or lignocaine, 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 coadministered 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.

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## Overdosage

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### ***Signs and 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 (refer to [Adverse reactions](#)).

### ***Management***

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

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## Pharmaceutical precautions

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### ***Instructions for use/handling***

Nil.

### ***Incompatibilities***

None known.

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

Store at or below 25°C. Protect from light and moisture.

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## Medicine classification

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Prescription Medicine.

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## Package quantities

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150 mg: packs of 60 tablets in cartoned blister strips.

300 mg: packs of 30 tablets in cartoned blister strips.

Not all pack sizes and/or strengths may be currently marketed.

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## Further information

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### ***List of excipients***

Microcrystalline cellulose, calcium hydrogen phosphate dihydrate, maize starch, sodium starch glycollate, magnesium stearate, silicon dioxide, titanium dioxide, lactose, hydroxypropylmethylcellulose, polyethylene glycol.

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## Name and address

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**Date of preparation**

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21 January 2010