AUSTRALIAN PRODUCT INFORMATION
CHEMMART RANITIDINE (RANITIDINE HYDROCHLORIDE) TABLETS

1 NAME OF THE MEDICINE

Ranitidine hydrochloride.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains ranitidine 150 mg or 300 mg.

For the full list of excipients see section **6.1 List of Excipients.**

3 PHARMACEUTICAL FORM

Ranitidine 150 mg tablets

White to off-white, round, biconvex tablets. Scored on one side and engraved “RAN” over “150” on the other side.

Ranitidine 300 mg tablets

White to off-white, capsule-shaped, biconvex tablets. Scored on one side and engraved “RAN 300” on the other side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Duodenal Ulcer

Short-term treatment of proven duodenal ulcer.

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

Gastric Ulcer

Short-term treatment of proven gastric ulcer.

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

Reflux Oesophagitis

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

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

Scleroderma Oesophagitis

Treatment of scleroderma oesophagitis.

Zollinger-Ellison Syndrome

Treatment of gastrinoma (Zollinger-Ellison syndrome).

4.2 DOSE AND METHOD OF ADMINISTRATION

Chemmart Ranitidine tablets are intended for oral administration.

Dosage

It is not necessary to time the ranitidine dose in relation to meals.

Acute Duodenal Ulceration

Acute Treatment

300 mg taken orally as a single dose at bedtime, or 150 mg taken orally twice a day, in the morning and at bedtime. In most cases healing will occur in four weeks although a small number of patients may require an additional two to four weeks of therapy.

Maintenance Treatment

150 mg taken at night.

As smoking is associated with a higher rate of relapse of duodenal ulcer, 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

Acute Treatment

300 mg taken orally as a single dose at bedtime, or 150 mg taken orally twice a day, in the morning and at bedtime. In most cases healing will occur in four weeks although a small number of patients may require an additional two to four weeks of therapy.

Maintenance Treatment

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

Gastrinoma (Zollinger-Ellison Syndrome)

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

Reflux Oesophagitis

Acute Treatment

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

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

Maintenance Treatment

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

Renal impairment

In patients with renal impairment or renal failure, dosage should be reduced as accumulation of ranitidine can occur. Dosage adjustments may be necessary in some older individuals based on renal function.

4.3 CONTRAINDICATIONS

Ranitidine tablets are contraindicated in patients with a known hypersensitivity to ranitidine hydrochloride or any components in this preparation.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Bradycardia

Bradycardia has been reported rarely in association with rapid administration of ranitidine injection, usually in patients with factors predisposing to cardiac rhythm disturbances. Recommended rates of administration should not be exceeded.

Gastric Ulcer

Treatment with a histamine H_2-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 syrup, tablets or injection is instituted.

Gastric pH and Pneumonia

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

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_2-histamine receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07-2.48).

Use in hepatic impairment

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. Nevertheless, caution should be observed in patients with hepatic dysfunction since ranitidine is metabolised by the liver.

Higher Doses

The use of higher than recommended doses of intravenous H_2-antagonists has been associated with rises in hepatic enzymes when treatment has been extended beyond five days.

ALT levels were increased to twice the pretreatment levels following prolonged IV administration of ranitidine (see section **4.8 Adverse effects (Undesirable effects)**). Therefore it may be prudent to monitor AST and ALT in patients receiving IV treatment for 5 days or longer and in those with pre-existing liver diseases.

Use in renal impairment

Ranitidine is excreted via the kidneys. 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.

Tobacco Smoking

Tobacco smoking appears to contribute to an increased risk of developing peptic ulcer disease and may also impair ulcer healing or increase the risk of ulcer recurrence (see section **4.2 Dose and method of administration**).

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 did not reveal any undue untoward effects.

Porphyria

In patients with a history of acute 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.

Use in the elderly

Since malignancy is more common in the elderly, particular consideration must be given to this before therapy with ranitidine is instituted.

Elderly patients receiving NSAIDs concomitantly with ranitidine should be closely supervised.

Sporadic cases of drug interactions have been reported in elderly patients involving both hypoglycaemic drugs and theophylline. The significance of these reports cannot be determined at present, as controlled clinical trials with theophylline and ranitidine have shown no interaction (see section **4.5 Interactions with other medicines and other forms of interactions**).

Elderly patients may be at risk for confusional states and depression (see section **4.8 Adverse effects (Undesirable effects)**).

Ranitidine is known to be substantially excreted by the kidney and the risk of toxic reactions to this medicine may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, caution should be exercised in dose selection, and it may be useful to monitor renal function (see section **4.4 Special warnings and precautions for use - Use in renal impairment**).

Paediatric use

Experience with ranitidine preparations 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.

Inhibition of CYP450-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, 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.

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 ranitidine may be reduced. This effect is not seen if sucralfate is taken after an interval of at least two hours.

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 (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.

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

Category B1

The safety or 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 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 adverse events in clinical trials or in 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.

Body as a Whole

Anaphylaxis, chest pain (as part of a hypersensitivity reaction), fever (as part of a hypersensitivity reaction), headache (sometimes severe), hypotension (as part of a hypersensitivity reaction), malaise.

Cardiovascular

As with other H_2-receptor antagonists, rare reports of AV block, asystole, bradycardia, tachycardia and premature ventricular beats.

Endocrine

Controlled studies in animals and humans have shown no stimulation of any pituitary hormone by ranitidine, no antiandrogenic activity, and cimetidine induced gynecomastia and impotence in hypersecretory patients have resolved when ranitidine was substituted. However, occasional cases of gynecomastia 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.

Gastrointestinal

Abdominal discomfort/pain, constipation, diarrhoea, nausea/vomiting.

Haematological

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

Hepatic (see section 4.4 Special warnings and precautions for use)

Transient and reversible changes in 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.

Musculoskeletal

Rare reports of arthralgia and myalgia.

Central Nervous System

The following were reported rarely:

Malaise, dizziness, somnolence, insomnia and vertigo.

Rarely, cases of reversible mental confusion, agitation, 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.

Integumental

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

Other

The following cases were reported rarely:

Hypersensitivity reactions (e.g., fever, bronchospasm, anaphylactic shock, urticaria, vasculitis, angioneurotic oedema, hypotension, chest pain, rash, eosinophilia), small increases in serum creatinine, acute pancreatitis.

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 and contact Apotex Medical Information Enquiries/Adverse Drug Reaction Reporting on 1800 195 055.

4.9 OVERDOSE

Symptoms

There has been virtually no experience of overdosage with ranitidine injection and limited experience 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 Adverse effects (Undesirable effects)**).

Rapid bolus injection of 300 mg intravenously (six times the recommended dose which should be given slowly) caused dizziness and peripheral vasodilatation.

Treatment

Symptomatic and supportive therapy should be given as appropriate.

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 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Animal experiments both *in vitro* and *in vivo* have established that ranitidine is a selective, competitive antagonist of histamine at H_2-receptor sites. Ranitidine has no significant interaction at histamine H_1-receptors, muscarinic receptors or β-adrenoceptors. 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_2-receptors by ranitidine in humans. 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 4 and 9 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 50-100 ng/mL has an inhibitory effect upon stimulated gastric acid secretion of approximately 50%.

Inhibition of pentagastrin induced gastric acid secretion increases with dose, and is 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 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 7 days did not cause bacterial overgrowth in the stomach.

Pulse rate, blood pressure, electrocardiogram (ECG) and electroencephalogram (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 duodenal ulcer patients showed a significant decrease in basal thyroxine levels after four weeks of 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.

Clinical trials

No data available.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Peak plasma levels occur about 2-3 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. Bioavailability of ranitidine is approximately 50%. Serum protein binding of ranitidine in man is in the range 10-19%. The elimination half-life is approximately 2 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 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 oral or intravenous 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

- Microcrystalline cellulose
- magnesium stearate
- colloidal anhydrous silica
- hypromellose
- polydextrose
- titanium dioxide
- vanillin
- carnauba wax

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

Store below 25°C.

6.5 NATURE AND CONTENTS OF CONTAINER

Chemmart Ranitidine

150 mg tablets: Blister packs of 60. AUST R 121976.

300 mg tablets: Blister packs of 30. AUST R 121979.

Chemmart is a registered trade mark of Symbion Pty Ltd.

Not all pack sizes or strengths may be available.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

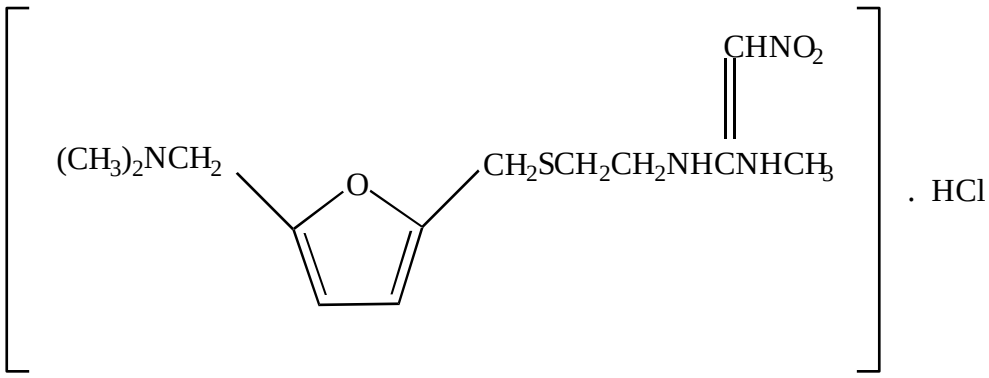
In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Ranitidine hydrochloride is a histamine H_2-receptor antagonist. It is an aminoalkyl substituted furan and is structurally different from cimetidine, lacking the imidazole ring and the cyanoguanidine group.

Ranitidine hydrochloride is a white or pale yellow crystalline powder with a slightly bitter taste and sulfur-like odour. Ranitidine hydrochloride is freely soluble in water and methanol and sparingly soluble in ethanol (96%).

Chemical structure



Chemical Name: N [2 [[[5 [(dimethylamino)methyl] 2 furanyl] methyl]thio]ethyl] N' methyl 2 nitro 1, 1 ethenediamine hydrochloride

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

Molecular Weight: 350.87

CAS number 66357-59-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription Only Medicine

8 SPONSOR

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9 DATE OF FIRST APPROVAL

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10 DATE OF REVISION

27 February 2019

Summary table of changes

Section Changed	Summary of new information
All	Reformatted product information; minor editorial changes
4.5, 4.8	Safety related changes.