NAME OF MEDICINE
Ranitidine hydrochloride.

Chemical Structure:

\[
\begin{array}{c}
\text{(CH}_3\text{)}_2\text{NCH}_2 \\
\text{CH}_2\text{SCH}_2\text{CH}_2\text{NCHNHCH}_3
\end{array}
\]

\[\text{CHNO}_2\cdot\text{HCl}\]

Formula: \(\text{C}_{13}\text{H}_{22}\text{N}_4\text{O}_3\text{S.HCl}\)

Chemical Name: \(\text{N} \left[\left[5 \left[(\text{dimethylamino})\text{methyl}\right] \text{2 furanyl}\right] \text{methyl}[\text{thio}]\text{ethyl}\right] \text{N'} \text{methyl} 2 \text{ nitro} 1, 1 \text{ethenediamine hydrochloride}\)

Molecular Weight: 350.87

CAS Registry Number: 66357-59-3

DESCRIPTION
Ranitidine hydrochloride is a histamine \(\text{H}_2\)-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%).

PHARMACOLOGY
Pharmacodynamics
Animal experiments both \textit{in vitro} and \textit{in vivo} have established that ranitidine is a selective, competitive antagonist of histamine at \(\text{H}_2\)-receptor sites. Ranitidine has no significant interaction at histamine \(\text{H}_1\)-receptors, muscarinic receptors or \(\beta\)-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 \(\text{H}_2\)-receptors by ranitidine in humans. Oral or intravenous administration of ranitidine inhibits both daytime and nocturnal basal gastric secretions and gastric acid secretion induced by histamine, food, pentagastrin and other secretagogues. On a weight basis ranitidine is between 4 and 9 times more potent than cimetidine.

Following oral administration of ranitidine in oral doses up to 300 mg, the plasma concentrations of ranitidine achieved are directly related to the dose administered. Stimulation of gastric acid secretion is inhibited by 50% with a plasma ranitidine concentration of 50-100 nanogram/mL.
The inhibition of pentagastrin induced gastric acid secretion increases with dose. Pentagastrin induced gastric acid secretion is inhibited by approximately 90% two hours after a single oral 150 mg dose and a significant effect is still evident twelve hours after this dose. In 10 patients with duodenal ulcer, ranitidine 150 mg given orally every twelve 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%.

Ranitidine has no significant effect on pentagastrin-stimulated intrinsic factor secretion.

Pepsin secretion is also inhibited by ranitidine, but secretion of gastric mucus is not affected. The secretion of bicarbonate or enzymes from the pancreas in response to secretin and pancreozymin is not altered by ranitidine.

Bacterial overgrowth in the stomach did not occur following a reduction in gastric acid secretion induced by ranitidine 150 mg twice daily for 7 days.

Following recommended doses of ranitidine pulse rate, blood pressure, electrocardiogram (ECG) and electroencephalogram (EEG) were not significantly affected in humans.

Ranitidine administered in recommended oral or intravenous (IV) dosage had no effect on serum prolactin levels.

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 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.

**Pharmacokinetics**

**Absorption**

Following oral administration of ranitidine tablets, ranitidine is rapidly absorbed with mean peak plasma levels of 1.5 μg/mL occurring approximately 3 hours after a single 300 mg dose. Food or concurrent antacid administration does not significantly alter absorption of ranitidine. Bioavailability of orally administered ranitidine is approximately 50% compared to an IV injection.

Following a single oral dose of 150 mg, serum concentrations of ranitidine necessary to inhibit 50% of stimulated gastric acid secretion (range 36 to 94 nanogram/mL) are maintained for up to 12 hours (see PHARMACOLOGY). However, blood levels bear no consistent relationship to dose or degree of acid inhibition.

**Distribution**

In humans, protein binding of ranitidine in serum is in the range of 10 to 19%.

**Excretion**

The principal route of excretion of ranitidine is via the kidneys. Ranitidine is excreted mainly as unchanged drug and in minor amounts as the principal metabolite N-oxide (< 4% of dose) as well as S-oxide (1%), desmethyl ranitidine (1%), and the furoic acid analogue (1%). Following oral administration of the drug, the 24 hour urinary recovery of free ranitidine and its metabolites is about 40%. The remainder of the administered dose is found in the stools.

The elimination half-life of ranitidine in humans is approximately 2 to 3 hours.

Impairment of renal function requires a reduction in dosage (see PRECAUTIONS).

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 (see PRECAUTIONS).
**INDICATIONS**

**Duodenal Ulcer**
Ranitidine is indicated for short-term treatment of proven duodenal ulcer.

Ranitidine is indicated for maintenance treatment to reduce the risk of relapse in duodenal ulcer.

**Gastric Ulcer**
Ranitidine is indicated for short-term treatment of proven gastric ulcer.

Ranitidine is indicated for 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**
Ranitidine is indicated for short-term symptomatic treatment of reflux oesophagitis unresponsive to conservative antireflux measures and simple drug therapies such as antacids.

Ranitidine is also indicated for maintenance treatment to reduce the risk of relapse of reflux oesophagitis.

**Scleroderma Oesophagitis**
Ranitidine is indicated for the treatment of scleroderma oesophagitis.

**Zollinger-Ellison Syndrome**
Ranitidine is indicated for treatment of gastrinoma (Zollinger-Ellison syndrome).

**CONTRAINDICATIONS**

Terry White Chemists Ranitidine tablets are contraindicated in patients with a known hypersensitivity to ranitidine hydrochloride or any components in the Terry White Chemists Ranitidine tablet preparation.

**PRECAUTIONS**

**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.

**Patients on Mechanical Ventilation**
In intubated intensive care unit patients receiving mechanical ventilation, agents that elevate gastric pH may increase the already present risk of nosocomial pneumonia.

**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).
Impaired Hepatic Function
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.

Increased Liver Enzymes
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 ADVERSE 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.

Impaired Renal Function
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 DOSAGE AND 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 has not revealed any undue untoward effects.

Porphyria
In patients with a history of acute porphyria, rare clinical reports suggest that ranitidine may precipitate acute porphyrnic attacks. Ranitidine should therefore be avoided in these patients.

Use in Pregnancy (Category B1$^1$)
The safety or ranitidine in pregnancy has not been established. Reproduction studies in rats and rabbits have revealed no evidence of impaired fertility or harm to the foetus due to ranitidine. 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 weighted 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 breast feeding mothers if considered essential.

Use in Children
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.

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.

$^1$ Drugs 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 fetus having been observed. Studies in animals have not shown evidence of an increased occurrence of fetal damage.
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 Interactions with Other Medicines).

Elderly patients may be at risk for confusional states and depression (see ADVERSE 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 PRECAUTIONS, Impaired Renal Function).

Interactions with Other Medicines

Inhibition of CYP450-linked mixed function oxygenase system
Ranitidine at therapeutic doses does not potentiate the actions of drugs which are inactivated by this enzyme; these include 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).

In a ranitidine-triazolam drug-drug interaction study, triazolam plasma concentrations were higher during b.i.d. dosing of ranitidine than triazolam given alone. The mean area under the triazolam concentration-time curve (AUC) values in 18- to 60- year-old subjects were 10% and 28% higher following administration of 75 mg and 150 mg ranitidine tablets, respectively, than triazolam given alone. In subjects older than 60 years of age, the mean AUC values were approximately 30% higher following administration of 75 mg and 150 mg ranitidine tablets. It appears that there were no changes in pharmacokinetics of triazolam and α-hydroxytriazolam, a major metabolite, and in their elimination. Reduced gastric acidity due to ranitidine may have resulted in an increase in the availability of triazolam. The clinical significance of this triazolam and ranitidine pharmacokinetic interaction is unknown.

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 2 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 presence of Zollinger-Ellison syndrome) may reduce the excretion of procainamide and N-acetylprocainamide resulting in increased plasma levels of these drugs.

ADVERSE EFFECTS
The following have been reported as adverse events in clinical trials and in routine management involving patients being treated with ranitidine. The relationship to ranitidine therapy has not been clear in many cases.

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 H₂-receptor antagonists, rare reports of AV block, asystole, bradycardia, tachycardia and premature ventricular beats have been noted following administration of ranitidine.

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, 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 (may be antibiotic associated if amoxycillin and metronidazole are also being taken), nausea, acute pancreatitis, vomiting. Acute pancreatitis has been reported rarely.

Haematological
Rare reports of agranulocytosis or pancytopaenia, sometimes with marrow hypoplasia or aplasia, aplastic anaemia and exceedingly rare cases of acquired immune haemolytic anaemia and eosinophilia (as part of a hypersensitivity reaction) have been reported. Blood count changes (leukopaenia, granulocytopenia, thrombocytopenia) have occurred in a few patients. These are usually reversible.

Hepatic (see PRECAUTIONS)
Transient and reversible changes in liver function tests can occur (see ADVERSE EFFECTS, Metabolic and Nutritional). There have been occasional reports of hepatitis, hepatocellular or hepatocanalicular or mixed, with or without jaundice. These were usually reversible, but in rare circumstances death has occurred. Rare cases of hepatic failure have also been reported. In rare SGPT (ALT) values were increased to at least twice the pretreatment levels in 6 of 12 subjects receiving 100 mg q.i.d. intravenously for 7 days, and in 4 of 245 subjects receiving 50 mg q.i.d. intravenously for 5 days.

Renal
Very rare cases of acute interstitial nephritis have been reported.

Metabolic and Nutritional
In normal volunteers, ALT values were increased to at least twice the pretreatment 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 (see PRECAUTIONS).

Musculoskeletal
Rare reports of arthralgia and myalgia.

Central Nervous System
Rarely, malaise, dizziness, somnolence, insomnia and vertigo. Rare 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.

Respiratory
Bronchospasm (as part of a hypersensitivity reaction).

Skin and Appendages
Rash including rare cases of mild erythema multiforme have been reported. Rarely, vasculitis and alopecia. As part of hypersensitivity reactions, rare cases of rash, urticaria, vasculitis and angioneurotic oedema have been reported.
Other
Small increases in serum creatinine.

DOSAGE AND ADMINISTRATION
Terry White Chemists Ranitidine tablets are administered by mouth. 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.

Impaired Renal Function
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.

OVERDOSAGE
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 Adverse Effects). In addition, abnormalities of gait and hypotension have been reported.
Rapid bolus injection of 300 mg intravenously (six times the recommended dose which should be given slowly) caused dizziness and peripheral vasodilatation.

**Treatment**
Activated charcoal may reduce absorption of the drug if given within one or two hours after ingestion. In patients who are not fully conscious or have impaired gag reflex, consideration should be given to administering activated charcoal via a nasogastric tube, once the airway is protected.

Institute supportive therapy for the evolving clinical syndrome.

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

**Contact the Poison Information Centre on 13 11 26 (Australia) for advice on the management of overdosage.**

**PRESENTATION AND STORAGE CONDITIONS**
Terry White Chemists Ranitidine 150 mg tablets in blister packs of 60: white to off-white, round, biconvex tablets. Scored on one side and engraved “RAN” over “150” on the other side. AUST R 121975.

Terry White Chemists Ranitidine 300 mg tablets in blister packs of 30: white to off-white, capsule-shaped, biconvex tablets. Scored on one side and engraved “RAN 300” on the other side. AUST R 121978.

Terry White Chemists Ranitidine tablets are intended for oral administration. Each tablet contains ranitidine 150 mg or 300 mg. The excipients in Terry White Chemists Ranitidine tablets are: cellulose-microcrystalline, magnesium stearate, silica-colloidal anhydrous, hypromellose, polydextrose, titanium dioxide, vanillin and carnauba wax.

Store below 25°C.

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**POISON SCHEDULE OF THE MEDICINE**
S4 – Prescription Only Medicine

**Date of TGA approval**: 27 September 2006

**Date of most recent amendment**: 2 February 2009