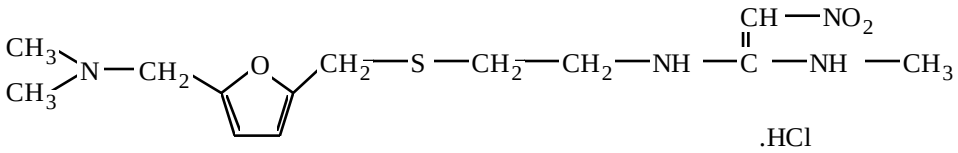
PRODUCT INFORMATION
RANITIDINE SANDOZ 150 MG AND 300 MG TABLETS

NAME OF THE MEDICINE

Generic name: Ranitidine hydrochloride.
Chemical name: N-(2-(((5-[(dimethylamino)methyl]-2-furanyl)methyl)thio)ethyl)-N'-methyl-2-nitro-1,1-ethenediamine hydrochloride.



.HCl

CAS [66357-59-3] $C_{13}H_{23}ClN_4O_3S$ MW: 350.9

DESCRIPTION

A white to pale or slightly yellow crystalline powder, freely soluble in water and in methanol, sparingly soluble in ethanol, very slightly soluble in methylene chloride. It exhibits polymorphism.

Ranitidine Sandoz tablets also contain the inactive ingredients: microcrystalline cellulose, calcium hydrogen phosphate, maize starch, sodium starch glycollate type A, magnesium stearate, colloidal anhydrous silica, lactose, hypromellose, titanium dioxide, macrogol 4000, iron oxide yellow .

PHARMACOLOGY

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 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_2-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 150mg dose and a significant effect is still evident twelve hours after this dose. In ten patients with duodenal ulcer, ranitidine 150mg given orally every twelve hours significantly reduced mean 24 hour hydrogen ion activity by 69% and nocturnal gastric acid output by 90%, whereas cimetidine (200mg three times daily and 400mg 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 150mg 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 (300mg/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 300mg daily, but no significant change in thyroid stimulating hormone was noted.

Pharmacokinetics

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.
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.

Patients over 50 years of age
In patient 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 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 ranitidine appears necessary in patients with hepatic impairment.

CLINICAL TRIALS

N/A

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 antireflux measures and simple drug therapies such as antacids.

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

Treatment of scleroderma oesophagitis.

CONTRAINDICATIONS

Known hypersensitivity to ranitidine or to any component of the preparation.

PRECAUTIONS

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 H2 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:

<u>Gastric ulcer</u>
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 tablets 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 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.

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

Use in pregnancy
Australian Pregnancy Category B1: 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 are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

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 fetus.

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

Paediatric use
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 150mg twice daily.

INTERACTIONS WITH OTHER MEDICINES

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. ketaconazole, atazanavir, delaviridine, gefitnib).

If high doses (2g) 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.

ADVERSE 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.

<u>Central nervous system</u>
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_2-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.

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 antiandrogenic 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, rash or uticaria, angioneurotic oedema, hypotension, chest pain, eosinophilia), small increases in serum creatinine. Acute pancreatitis has been reported rarely.

DOSAGE AND ADMINISTRATION

Ranitidine Sandoz is an oral tablet.

Duodenal or gastric ulceration
Acute treatment. 300mg taken as a single dose at bedtime, or 150mg 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 of therapy.

Maintenance treatment. Duodenal ulcer: 150mg 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 300mg at night provides additional therapeutic benefit.

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

Gastrinoma (Zollinger-Ellison syndrome)
150mg taken three times daily initially and increased, as necessary, to 600 to 900mg/day.

Oesophagitis
300mg taken as a single dose at bedtime or 150mg 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 300mg, taken as a single dose at bedtime, has been established for treatment periods of up to three months.

Maintenance treatment. Reflux oesophagitis: 150mg taken twice daily, in the morning and at bedtime.

OVERDOSAGE

Symptoms
There has been limited experience of overdosage 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 ADVERSE EFFECTS).

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

Contact the Poisons Information Centre on 13 11 26 for advice on management of an overdose.

PRESENTATION AND STORAGE CONDITIONS

Ranitidine Sandoz 150mg Tablets: yellow, round, film-coated tablets, scored on one side. Available in Al/Al blisters in packs of 60 tablets.

Ranitidine Sandoz 300mg Tablets: yellow, oblong, film-coated tablets, scored on one side. Available in Al/Al blisters in packs of 30 tablets.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Sandoz Pty Ltd
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POISON SCHEDULE OF THE MEDICINE

Schedule 4 – Prescription Only Medicine

Date of first inclusion in the Australian Register of Therapeutic Goods (the ARTG): 03/08/1999

Date of most recent amendment: 21/01/2016