PRODUCT INFORMATION

AUSRAN

(150 mg and 300 mg TABLETS)

NAME OF THE MEDICINE

AUSRAN tablets contain ranitidine hydrochloride. Its chemical structure is represented below:

![Chemical Structure](image)

CAS No.: 66357-59-3

Empirical Formula: C_{13}H_{22}N_{4}O_{3}S.HCl.

MW: 350.9

DESCRIPTION

Ranitidine hydrochloride is an aminoalkyl substituted furan and is structurally different from cimetidine, lacking the imidazole ring and the cyanoguanidine group.

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

AUSRAN is available in 150 mg and 300 mg tablets. Each tablet contains ranitidine hydrochloride equivalent to 150 mg or 300 mg of ranitidine respectively. Each tablet also contains the following excipients: cellulose - microcrystalline, croscarmellose sodium, magnesium stearate, OPADRY II complete film coating system YS-22-18096 White (USA).

PHARMACOLOGY

AUSRAN is a histamine H_{2}-receptor antagonist.

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 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 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 twelve hours after this dose. In ten 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%.

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, electrocardiogram and electroencephalogram 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. 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**

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.

**Distribution and Metabolism**

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.
Excretion
Ranitidine is excreted via the kidneys mainly as unchanged drug and in minor amounts as the N-oxide, S-oxide and desmethyl metabolites. The 24 hour urinary recovery of free ranitidine and its metabolites is about 40% after oral administration of the drug.

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.

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 hydrochloride or any of the excipients listed under DESCRIPTION.

PRECAUTIONS

Gastric ulcer
Treatment with a histamine H₂-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.

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 H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07 – 2.48).

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 Pregnancy (Category B1)
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 fetus due to ranitidine. Ranitidine crosses the placenta. Ausran 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 is secreted in breast milk in lactating mothers but the clinical significance of this has not been fully evaluated. Ausran should only be used by nursing mothers if considered essential.

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 150 mg twice daily.

INTERACTIONS WITH OTHER MEDICINES
Although ranitidine has been reported to bind weakly to cytochrome P450 in vitro, recommended doses of the drug do not inhibit the action of the cytochrome P450 linked oxygenase in the liver.

There are conflicting reports in the literature about possible interactions between ranitidine and several drugs; the clinical significance of these reports has not been substantiated.

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.
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.

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 H₂-receptor antagonists, rare reports of tachycardia, bradycardia, premature ventricular beats, atrioventricular block and asystole.

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

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.

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

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 gynaecomastia, 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 have been reported.

Other. Rare cases of hypersensitivity reactions (e.g. fever, bronchospasm, anaphylactic shock, rash, eosinophilia, urticaria, angioneurotic oedema, hypotension, chest pain), small increases in serum creatinine. Acute pancreatitis has been reported rarely.
DOSAGE AND 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 of 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.
Reflux oesophagitis: 150 mg taken twice daily, in the morning and at bedtime.

OVERDOSAGE

For information on the management of overdose, contact the Poison Information Centre on 131126.

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 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.
PRESENTATION AND STORAGE CONDITIONS

**AUSRAN 150 mg tablets:** Each tablet is white, round, biconvex, film coated, embossed with ‘150’ on one side and plain on the other, and contains ranitidine hydrochloride equivalent to 150 mg of ranitidine. The tablets are supplied in a blister pack of 60 tablets, or as a bottle of 60 tablets* or 180 tablets*.

**AUSRAN 300 mg tablets:** Each tablet is white, oblong, biconvex, film coated, embossed with ‘300’ on one side and plain on the other, and contains ranitidine hydrochloride equivalent to 300 mg of ranitidine. The tablets are supplied in a blister pack of 30 tablets, or as a bottle of 30 tablets* or 90 tablets*.

* Not currently marketed in Australia.

Store below 25°C. Protect from light.

NAME AND ADDRESS OF THE SPONSOR

Arrow Pharma Pty Ltd
15-17 Chapel Street
Cremorne VIC 3121

POISON SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine).

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

AUSRAN 150 mg/300 mg tablets blister pack: 7 October 2003
AUSRAN 150 mg/300 mg tablets bottle: 3 August 2004

DATE OF MOST RECENT AMENDMENT

5 July 2016