Tacidine
Nizatidine

PRODUCT INFORMATION

NAME OF THE MEDICINE

Active Ingredient: Nizatidine

Chemical name: N-[2-[[2-(dimethylamino)methyl]-4-thiazolyl]-methyl]thio-ethyl]-N'-methyl-2-nitro-1,1-ethenediamine.

Structural formula:

![Structural formula of Nizatidine]

Molecular formula: C₁₂H₂₁N₅O₂S₂

Molecular weight: 331.46

CAS Registry no.: 76963-41-2

DESCRIPTION

Nizatidine is an off-white to buff crystalline solid that is sparingly soluble in water. Pharmacologically, it is a histamine, H₂-receptor antagonist.

Tacidine capsules are for oral administration and contain either 150 mg or 300 mg of the active ingredient, nizatidine. The capsules also contain the following inactive excipients; croscarmellose sodium, starch-pregelatinised maize, purified talc, magnesium stearate, quinoline yellow CI47005 (150 mg only), allura red AC CI16035 (150 mg only), iron oxide yellow CI77492, iron oxide red CI77491 (300 mg capsule only), titanium dioxide, gelatin and black ink SW-9008/ SW-9009.

PHARMACOLOGY

Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H₂-receptors, particularly those in the gastric parietal cells.

Antisecretory Activity

Effects on Acid Secretion. Nizatidine significantly inhibits basal and nocturnal gastric-acid secretion for up to 12 hours. Nizatidine also significantly inhibits gastric-acid secretion stimulated by food, caffeine, betazole, and pentagastrin in a dose dependent manner. Rebound hypersecretion of gastric acid may occur after cessation of the drug.

Effects on Other Gastrointestinal Secretions – Pepsin. Oral administration of 75 to 300 mg of nizatidine does not affect pepsin activity in gastric secretions. Total pepsin output is reduced in proportion to the reduced volume of gastric secretions.

Intrinsic Factor. Intrinsic factor is not decreased in subjects administered nizatidine.

Serum Gastrin. Nizatidine has no effect on basal serum gastrin. No rebound of gastrin secretion was observed when food was ingested 12 hours after administration of nizatidine.
Other Pharmacologic Actions

Hormones. Nizatidine was not shown to affect the serum concentrations of gonadotropins, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxine, testosterone, 5α-dihydrotestosterone, androstenedione, or oestradiol. With acute nizatidine administration, transient increases in serum prolactin have been observed in male animals.

Nizatidine had no demonstrable anti-androgenic action.

Pharmacokinetics

The onset is half an hour while the duration of action is up to 12 hours. The absolute oral bioavailability of nizatidine exceeds 70%. Peak plasma concentrations (700 to 1,800 mcg/L for a 150 mg dose and 1,400 to 3,600 mcg/L for a 300 mg dose) occur from 0.5 to 3 hours following the dose. A concentration of 1,000 mcg/L is equivalent to 3 mmol/L; a dose of 300 mg is equivalent to 905 mmoles. Plasma concentrations 12 hours after administration are less than 10 mcg/L. The elimination half-life is 1 to 2 hours, plasma clearance is 40 to 60 L/h, and the volume of distribution is 0.8 to 1.5 L/kg. Because of the short half-life and rapid clearance of nizatidine, accumulation of the drug would not be expected in individuals with normal renal function who take either 300 mg once daily in the evening or 150 mg twice daily. Nizatidine exhibits dose proportionality over the recommended dose range.

The oral bioavailability of nizatidine is unaffected by concomitant ingestion of propantheline. Antacids consisting of aluminium and magnesium hydroxides with simethicone decrease the absorption of nizatidine by about 10%. With food the AUC and Cmax increase by approximately 10%.

Charcoal has also been shown to reduce oral bioavailability of nizatidine. This reduction is in the range of 20 to 25%.

Less than 7% of an oral dose is metabolised as N2-monodesmethyl-nizatidine, an H2-receptor antagonist, which is the principal metabolite excreted in the urine. Other likely metabolites are the N2-oxide (less than 5% of the dose) and the S-oxide (less than 6% of the dose).

More than 90% of an oral dose of nizatidine is excreted in the urine within 12 hours. About 60% of an oral dose is excreted as unchanged drug. Renal clearance is about 500 mL/min, which indicates excretion by active tubular secretion. Less than 6% of an administered dose is eliminated in the faeces.

Moderate to severe renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In individuals who are functionally anephric, the half-life is 3.5 to 11 hours, and the plasma clearance is 7 to 14 L/h. To avoid accumulation of the drug in individuals with clinically significant renal impairment, the amount and/or frequency of doses of nizatidine should be reduced in proportion to the severity of dysfunction (see Dosage and Administration).

Approximately 35% of nizatidine is bound to plasma protein, mainly to alpha 1-acid glycoprotein. Warfarin, diazepam, paracetamol, propantheline, phenobarbitone, and propranolol did not affect plasma protein binding of nizatidine in vitro.

CLINICAL TRIALS

1. Active Duodenal Ulcer. In multicentre, double-blind, placebo-controlled studies, endoscopically diagnosed duodenal ulcers healed more rapidly following administration of nizatidine, 300 mg at bedtime or 150 mg twice daily, than with placebo. Lower doses, such as 100 mg at bedtime, had slightly lower effectiveness.

2. Maintenance of Healed Duodenal Ulcer. In multicentre, double-blind, comparator controlled studies, the healing rates following the administration of nizatidine (N=388) were 81% within 4 weeks and 92% within 8 weeks.
Treatment with a reduced dose of nizatidine has been shown to be effective as maintenance therapy following healing of active duodenal ulcers. In multicentre, double-blind, placebo-controlled studies, 150 mg of nizatidine taken in the evening resulted in a significantly lower incidence of duodenal ulcer recurrence in patients treated for up to 1 year.

3. **Benign Gastric Ulcer.** In multicentre, double-blind, comparator controlled studies, patients received nizatidine 150 mg twice daily or nizatidine 300 mg in the evening. Healing rates in both dosage groups (66.2% and 65.2%, respectively) were not statistically different. Analysis of symptomatic responses showed that 68-76% of patients were symptom free after 4 weeks therapy.

4. **Gastro-oesophageal Reflux Disease (reflux oesophagitis).** In multicentre, double-blind, placebo-controlled clinical trials, nizatidine was more effective than placebo in improving endoscopically diagnosed oesophagitis and in healing erosive and ulcerative oesophagitis.

In a study in patients with erosive or ulcerative oesophagitis, nizatidine, 150 mg twice daily, compared with placebo, yielded a higher healing rate at 3 weeks (16% vs 7%) and at 6 weeks (32% vs 16%, p<0.05). In another study, nizatidine, 150 mg twice daily, compared to placebo treatment, showed a higher healing rate at 6 weeks (21% vs 11%, p<0.05) and at 12 weeks (29% vs 13%, p<0.01).

In addition, relief of associated heartburn was greater in patients treated with nizatidine. Patients treated with nizatidine consumed fewer antacids than did patients treated with placebo.

**INDICATIONS**

Tacidine is indicated for up to 8 weeks for the treatment of active duodenal ulcer. In most patients, the ulcer will heal within 4 weeks.

Tacidine is also indicated for maintenance therapy for duodenal ulcer patients, at a reduced dosage of 150 mg at bedtime, after healing of the active duodenal ulcer. Continuous therapy with nizatidine for longer than 1 year has not been studied.

Tacidine is indicated for up to 8 weeks for the treatment of benign gastric ulcer.

Tacidine is indicated for up to 12 weeks for the treatment of oesophagitis, including erosive and ulcerative oesophagitis and associated heartburn due to reflux.

**CONTRAINDICATIONS**

Nizatidine is contraindicated in patients with known hypersensitivity to the drug, and because cross sensitivity in this class of compounds has been observed, nizatidine should not be administered to patients with a history of hyper-sensitivity to other H₂-receptor antagonists.

**PRECAUTIONS**

**Gastric malignancy**

Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

**Renal Impairment**

Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see DOSAGE AND ADMINISTRATION).
Hepatic Impairment

Pharmacokinetic studies in patients with hepato-renal syndrome have not been done. Part of the dose of nizatidine is metabolised in the liver. Nizatidine cannot be recommended in patients with hepatic failure. In patients with normal renal function and uncomplicated hepatic dysfunction, the disposition of nizatidine is similar to that in normal subjects.

Nosocomial pulmonary infections

There is a possibility of nosocomial pulmonary infections associated with bacterial colonisation of the stomach in patients in Intensive Care Units receiving drugs which suppress acid secretion.

Carcinogenicity, Mutagenicity, Impairment of Fertility

A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day (about 80 times the recommended daily therapeutic dose) showed no evidence of a carcinogenic effect. There was a dose related increase in the density of enterochromaffin-like (ECL) cells in the gastric oxyntic mucosa. In a two year study in mice, there was no evidence of a carcinogenic effect in male mice; although hyperplastic nodules of the liver were increased in the high dose males as compared to placebo. Female mice given the high dose of nizatidine (2,000 mg/kg/day, about 330 times the human dose) showed marginally statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups. The rate of hepatic carcinoma in the high dose animals was within the historical control limits seen for the strain of mice used. The female mice were given a dose higher than the maximum tolerated dose, as indicated by excessive (30%) weight decrement as compared with concurrent controls, and evidence of mild liver injury (transaminase elevations). The occurrence of a marginal finding at high dose only in animals given an excessive, and somewhat hepatotoxic dose, with no evidence of a carcinogenic effect in rats, male mice, and female mice (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for nizatidine.

Nizatidine was not mutagenic in a battery of tests performed to evaluate its potential genetic toxicity, including bacterial mutation tests, unscheduled DNA synthesis, sister chromatid exchange, mouse lymphoma assay, chromosome aberration tests, and a micronucleus test.

In a 2-generation, perinatal and postnatal, fertility study in rats, doses of nizatidine up to 650 mg/kg/day produced no adverse effects on the reproductive performance of parental animals or their progeny.

Use in Pregnancy (Category B3)

Oral reproduction studies in rats at doses up to 1500 mg/kg, and in Dutch Belted rabbits at doses up to 275 mg/kg, revealed no evidence of impaired fertility or teratogenic-effect. At doses above 275 mg/kg treated rabbits had abortions, decreased number of live foetuses, and depressed foetal weights. On intravenous administration to pregnant New Zealand white rabbits, nizatidine at 20 mg/kg produced cardiac enlargement, coarctation of the aortic arch, and cutaneous oedema in 1 foetus and at 50 mg/kg it produced ventricular anomaly, distended abdomen, spina bifida, hydrocephaly, and enlarged heart in 1 foetus.

There are, however, no adequate and well-controlled studies in pregnant women. It is also not known whether nizatidine can cause foetal harm when administered to pregnant women or can affect reproduction capacity.

Nizatidine should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Use in Lactation

Studies conducted in lactating women have shown that 0.1% of the administered oral dose of nizatidine is secreted in human milk in proportion to plasma concentrations. Because of the growth depression in pups reared by lactating rats treated with nizatidine, a decision should be made whether to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.
Paediatric Use

Safety and effectiveness in children have not been established.

Use in the Elderly

Ulcer healing rates in elderly patients are similar to those in younger age groups. The incidence rates of adverse events and laboratory test abnormalities are also similar to those seen in other age groups. Age alone may not be an important factor in the disposition of nizatidine. Nizatidine is known to be substantially excreted by the kidney, and the toxic reactions to this drug may be greater in patients with impaired renal function. Elderly patients are more likely to have reduced renal function. Care should be taken in the dose selection in this patient group and may be useful to monitor renal function (see DOSAGE AND ADMINISTRATION).

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 that had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CI, 1.07-2.48).

Effects on Laboratory Tests

False-positive tests for urobilinogen with Multistix may occur during therapy with nizatidine.

INTERACTIONS WITH OTHER MEDICINES

No interactions have been observed between nizatidine and theophylline, chlordiazepoxide, lorazepam, lignocaine, phenytoin, warfarin, aminophylline, diazepam, and metoprolol. Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolising enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. However, nizatidine and other histamine H₂-receptor antagonists can reduce the gastric absorption of drugs whose absorption is dependent on an acidic gastric pH. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen when nizatidine, 150 mg twice daily, was administered concurrently.

ADVERSE EFFECTS

Nizatidine has been shown to be generally well tolerated. The safety profile is at least as good, if not better than, other H₂-receptor antagonists.

Placebo-controlled trials conducted included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in the placebo-controlled trials, anaemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group.

Hepatic. Hepatocellular injury, evidenced by elevated liver enzyme tests (SGOT [AST], SGPT [ALT], or alkaline phosphatase), occurred in some patients and was possibly or probably related to nizatidine. In some cases there was marked elevation of SGOT, SGPT enzymes (greater than 500 IU/L) and in a single instance SGPT was greater than 2,000 IU/L. The overall rate of occurrences of elevated liver enzymes and elevations to 3 times the upper limit of normal, however, did not significantly differ from the rate of liver enzyme abnormalities in placebo treated patients. All abnormalities were reversible after discontinuation of nizatidine.

Rare cases of hepatitis and jaundice and cholestatic or mixed hepato-cellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of nizatidine.

Cardiovascular. In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered nizatidine and in 3 untreated subjects.
CNS. Rare cases of reversible mental confusion have been reported.

Endocrine. Clinical pharmacology studies and controlled clinical trials showed no evidence of anti-androgenic activity due to nizatidine. Impotence and decreased libido were reported with equal frequency by patients who received nizatidine and by those given placebo. Rare reports of gynaecomastia occurred.

Haematologic. Anaemia was reported significantly more frequently in nizatidine (0.2%) than in placebo-treated (0%) patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another H₂ receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

Integumental. Sweating and urticaria were reported significantly more frequently in nizatidine than in placebo patients. Rash, exfoliative dermatitis and pruritis were also reported.

Hypersensitivity. As with other H₂-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Rare episodes of hypersensitivity reactions (e.g., bronchospasm, laryngeal oedema, rash, and eosinophilia) have been reported.

Body as a Whole. Serum sickness-like reactions have occurred rarely (in less than 1/1,000 patients) in conjunction with nizatidine use.

Genitourinary. Reports of impotence have occurred.

Other. Hyperuricaemia unassociated with gout or nephrolithiasis has been reported. Eosinophilia, fever and nausea related to nizatidine administration have been reported.

**DOSAGE AND ADMINISTRATION**

Active Duodenal Ulcer. The recommended oral dosage for adults is 150 mg twice daily or 300 mg once daily in the evening (for up to 8 weeks). In most cases, the ulcer will heal within 4 weeks.

Benign Gastric Ulcer. The recommended daily dose is 150 mg twice daily or 300 mg once daily in the evening (for up to 8 weeks). Prior to treatment with nizatidine, care should be taken to exclude the possibility of gastric cancer.

Maintenance Therapy. The recommended oral dosage for adults with duodenal ulcer is 150 mg once daily in the evening for a period not exceeding 12 months. Continuous therapy with nizatidine for longer than 12 months has not been studied.

Gastro-oesophageal Reflux Disease. The recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily (for up to 12 weeks).

Dosage Adjustment for Patients with Moderate to Severe Renal Insufficiency. The dose for patients with renal dysfunction should be reduced as follows:

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 to 50 mL/min</td>
<td>150 mg daily</td>
</tr>
<tr>
<td>&lt;20 mL/min</td>
<td>150 mg every 2 days</td>
</tr>
<tr>
<td>Maintenance Therapy (Duodenal Ulcer)</td>
<td></td>
</tr>
<tr>
<td>20 to 50 mL/min</td>
<td>150 mg every 2 days</td>
</tr>
<tr>
<td>&lt;20 mL/min</td>
<td>150 mg every 3 days</td>
</tr>
</tbody>
</table>

Some elderly patients may have creatinine clearances of less than 50 mL/min, and, based on pharmacokinetic data in patients with renal impairment, the dose for such patients should be reduced accordingly. The clinical effects of this dosage reduction in patients with renal failure have not been evaluated.
OVERDOSAGE

Overdoses with nizatidine have been reported rarely. The following is provided to serve as a guide should such an overdose be encountered.

**Signs and Symptoms.** There is little clinical experience with overdosage of nizatidine in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhoea. Single oral doses of 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal. Intravenous median lethal doses in the rat and mouse were 301 mg/kg and 232 mg/kg respectively.

**Treatment.** In managing overdosage, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdosage occurs, use of activated charcoal should be considered along with clinical monitoring and supportive therapy. Renal dialysis for 4 to 6 hours increased plasma clearance.

In cases of overdosage, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Tacidine 150; nizatidine 150 mg capsule – hard gelatin capsule with a pale yellow body and dark yellow cap. The body has “NZ 150” and the cap has “G” printed in black. Each bottle* or blister pack contains either 30* or 60 capsules.

Tacidine 300; nizatidine 300 mg capsule - hard gelatin capsule with a light brown body and cap. The body has “NZ 300” and the cap has “G” printed in black. Each bottle* or blister pack contains either 30 or 60* capsules.

* Not marketed in Australia.

Tacidine 150 and Tacidine 300 capsules should be stored below 25°C.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

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POISONS SCHEDULE OF THE MEDICINE

S4 (Prescription Only Medicine)
DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (the ARTG)

29/04/2003

DATE OF MOST RECENT AMENDMENT

04/07/2013