

# **AUSTRALIAN PRODUCT INFORMATION – NIZAC (NIZATIDINE) CAPSULES**

## **1 NAME OF THE MEDICINE**

Nizatidine

## **2 QUALITATIVE AND QUANTITATIVE COMPOSITION**

NIZAC (nizatidine) is a histamine H<sub>2</sub>-receptor antagonist.

Each capsule contains for oral administration either 150 mg or 300 mg of nizatidine as the active ingredient.

## **3 PHARMACEUTICAL FORM**

150 mg: Size 2 capsule consisting of a dark yellow cap and a pale yellow body, printed with "N150".

300 mg: Size 1 capsule consisting of a brown cap and a pale yellow body, printed with "N300".

## **4 CLINICAL PARTICULARS**

### **4.1 THERAPEUTIC INDICATIONS**

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

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

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

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

### **4.2 DOSE AND METHOD OF ADMINISTRATION**

Active Duodenal Ulcer--The recommended oral dosage for adults is 150 mg twice daily or 300 mg once daily in the evening.

Benign Gastric Ulcer--The recommended daily dose is 150 mg twice daily or 300 mg once daily in the evening. 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.

Gastroesophageal Reflux Disease--The recommended oral dosage in adults for the treatment of erosions, ulcerations, and associated heartburn is 150 mg twice daily.

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

<b>Creatine Clearance</b>	<b>Dose</b>
20 to 50 mL/min	150 mg daily
< 20 mL/min	150 mg every 2 days
<b>Maintenance Therapy (Duodenal Ulcer)</b>	
20 to 50 mL/min	150 mg every 2 days
< 20 mL/min	150 mg every 3 days

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.

### **4.3 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 hypersensitivity to other H<sub>2</sub>-receptor antagonists.

### **4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE**

#### **General**

1. 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.
2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).
3. 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.

4. 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.

### **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. Elderly patients may have reduced renal function (see Section 4.2 DOSE AND METHOD OF 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 histamine H2 receptor antagonists versus those who had stopped treatment, with an observed adjusted relative risk of 1.63 (95% CL, 1.07 – 2.48).

### **Paediatric use**

Safety and effectiveness in children have not been established.

### **Effects on laboratory tests**

False-positive tests for urobilinogen with Multistix<sup>®</sup> may occur during therapy with nizatidine.

## **4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS**

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 b.i.d., was administered concurrently.

## **4.6 FERTILITY, PREGNANCY AND LACTATION**

### **Effects on fertility**

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 – 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 nursing or discontinue the drug, taking into account the importance of the drug to the mother.

#### **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)**

Nizatidine has been shown to be generally well tolerated. The safety profile is at least as good as, if not better than, other H<sub>2</sub>-receptor antagonists. Worldwide, controlled clinical trials of nizatidine included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these 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 hepatocellular 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 antiandrogenic 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 (0%) treated patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another H<sub>2</sub> 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 H<sub>2</sub>-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 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.

### **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](http://www.tga.gov.au/reporting-problems).

## **4.9 OVERDOSE**

Overdoses of 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 overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.

If overdose 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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

## 5 PHARMACOLOGICAL PROPERTIES

### 5.1 PHARMACODYNAMIC PROPERTIES

#### **Mechanism of action**

Nizatidine is a competitive, reversible inhibitor of histamine at the histamine H<sub>2</sub>-receptors, particularly those in the gastric parietal cells.

#### Antisecretory Activity

1. 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.

2. 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:

- a. Hormones: Nizatidine was not shown to affect the serum concentrations of gonadotropins, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxine, testosterone, 5 -dihydrotestosterone, androstenedione, or oestradiol. With acute nizatidine administration, transient increases in serum prolactin have been observed in male animals.
- b. Nizatidine had no demonstrable antiandrogenic action.

## 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 h.s. or 150 mg b.i.d., than with placebo. Lower doses, such as 100 mg h.s., 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 B.D. or nizatidine 300 mg nocte. 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. Gastroesophageal 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 b.i.d., 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 b.i.d., 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.

## 5.2 PHARMACOKINETIC PROPERTIES

Onset and duration of action: half an hour, lasting up to 12 hours. The absolute oral bioavailability of nizatidine exceeds 70%. Peak plasma concentrations (700 to 1,800  $\mu\text{g/L}$  for a 150-mg dose and 1,400 to 3,600  $\mu\text{g/L}$  for a 300-mg dose) occur from 0.5 to 3 hours following the dose. A concentration of 1,000  $\mu\text{g/L}$  is equivalent to 3  $\mu\text{mol/L}$ ; a dose of 300 mg is equivalent to 905  $\mu\text{moles}$ . Plasma concentrations 12 hours after administration are less than 10  $\mu\text{g/L}$ . The elimination half-life is 1 to 1.5 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  $C_{max}$  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  $H_2$ -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 Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

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

### **5.3 PRECLINICAL SAFETY DATA**

#### **Genotoxicity**

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.

#### **Carcinogenicity**

A two-year oral carcinogenicity study in rats with doses as high as 500 mg/kg/day 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) 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 larger 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), and a negative mutagenicity battery are not considered evidence of a carcinogenic potential for nizatidine.

## **6 PHARMACEUTICAL PARTICULARS**

### **6.1 LIST OF EXCIPIENTS**

The 150 mg capsule also contains the following excipients: maize starch, pregelatinised maize starch, dimeticone 350, magnesium stearate, iron oxide yellow, titanium dioxide, sodium lauryl sulfate, gelatin and printing Ink OPACODE monogramming ink S-1-17823 BLACK (PI 12108).

The 300 mg capsule also contains the following excipients: maize starch, pregelatinised maize starch, povidone, croscarmellose sodium, dimeticone 350, purified talc, iron oxide red, iron oxide yellow, titanium dioxide, gelatin and printing Ink Tekprint SW-09008 black ink (PI 2328).

### **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**

NIZAC 150 mg capsules are available in Blister packs (PVC/Al) of 60 capsules.

NIZAC 300 mg capsules are available in Blister packs (PVC/Al) of 30 capsules.

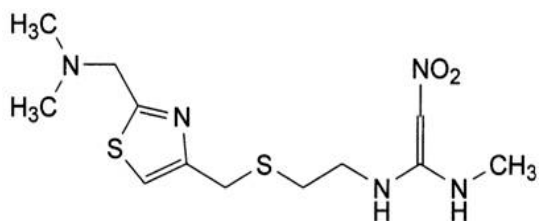
### **6.6 SPECIAL PRECAUTIONS FOR DISPOSAL**

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

### **6.7 PHYSICOCHEMICAL PROPERTIES**

Nizatidine is an off-white to buff crystalline solid that is sparingly soluble in water.

#### **Chemical structure**



#### CAS number

CAS No. of 76963-41-2

## 7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine.

## 8 SPONSOR

Arrow Pharma Pty Ltd  
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[www.arrowpharma.com.au](http://www.arrowpharma.com.au)

## 9 DATE OF FIRST APPROVAL

18 September 2003

## 10 DATE OF REVISION

29 January 2021

### SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	PI is reformatted