PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

PrAXID®

Nizatidine Capsules

Capsules 150 mg, 300 mg, Oral

USP

Histamine H_2 Receptor Antagonist

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

AXID (nizatidine capsules) is indicated for:

- the treatment of conditions where a controlled reduction of gastric acid secretion is required such as for ulcer healing and/or pain relief: acute duodenal ulcer, acute benign gastric ulcer, gastroesophageal reflux disease and prophylactic use in duodenal ulcer.

1.1 Pediatrics

Pediatrics (under 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (over 65 years of age): Evidence from clinical studies and experience do not suggest that use in the geriatric population is associated with differences in safety or effectiveness.

Age alone is not an important factor in determining the disposition of nizatidine; however elderly patients may have reduced renal function. See 4 DOSAGE AND ADMINISTRATION; 7.4 WARNINGS AND PRECAUTIONS, Geriatrics; and 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Elimination.

2 CONTRAINDICATIONS

- AXID is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.
- AXID is contraindicated in patients with a history of previous hypersensitivity to other H_2-receptor antagonist agents (cross sensitivity in this class of compounds has been observed).

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

Duodenal or Gastric Ulcer: One 300 mg capsule or two 150 mg capsules once daily at bedtime. Alternatively, 150 mg twice daily may be used. Healing occurs within 4 weeks in most cases of

duodenal ulcer; but if healing is not documented or has not occurred, therapy should be given for 8 weeks.

Maintenance Therapy in Duodenal Ulcer: One 150 mg capsule once daily at bedtime for 6 - 12 months depending on the severity of the condition.

Gastroesophageal Reflux Disease: One 150 mg capsule twice daily for the treatment of erosions, ulcerations and associated heartburn.

Antacids may be given concomitantly if needed.

Dose Adjustment in Renal Impairment

Renal Function	Creatinine Clearance (mL/min.)	Dosage	
		Acute	Maintenance
Normal	> 50	300 mg/day	150 mg/day
Moderate Impairment	20-50	150 mg/day	150 mg/2nd day
Severe Impairment	< 20	150 mg/2nd day	150 mg/3rd day

4.4 Administration

Take this medicine with a full glass of water.

4.5 Missed Dose

Take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.

5 OVERDOSAGE

There is little clinical experience with deliberate overdosage of nizatidine in humans. Test animals that received large doses of nizatidine have exhibited cholinergic-type effects, including lacrimation, salivation, emesis, miosis, and diarrhea. Should overdosage occur, use of activated charcoal, emesis, or lavage should be considered along with clinical monitoring and supportive therapy. Renal dialysis does not substantially increase clearance of nizatidine due to its large volume of distribution.

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Oral	Capsules 150 mg	Corn starch, magnesium stearate, pregelatinized starch and silicon fluid. The printed capsule shells contain also benzyl alcohol, butylparaben, calcium disodium edetate, carboxy-methylcellulose sodium, gelatin, iron oxide black, iron oxide yellow, methylparaben, potassium hydroxide, propylparaben, shellac, sodium lauryl sulfate, sodium propionate and titanium dioxide
Oral	Capsules 300 mg	Corn starch, carboxymethylcellulose sodium, pregelatinized starch, povidone, silicon fluid and talc. The printed capsule shells contain also benzyl alcohol, butylparaben, calcium disodium edetate, gelatin, iron oxide black, iron oxide red, iron oxide yellow, methylparaben, potassium hydroxide, propylparaben, shellac, sodium lauryl sulfate, sodium propionate and titanium dioxide

Capsules 150 mg: Hard gelatin size #2 capsules with an opaque yellow cap and a lighter yellow opaque body. Capsules are printed in black ink; the cap is printed “ab” and the body is printed “N 150”. Capsules are filled with light yellow powder. Capsules contain 150 mg nizatidine and are available in natural HDPE bottles of 100.

Capsules 300 mg: Hard gelatin size#1 capsules with an opaque brown cap and an opaque yellow body. Capsules are printed in black ink with “AXID over 300 mg” on one half and “AXID over 3145” on the other. Capsules are filled with light yellow powder. Capsules contain 300 mg nizatidine and are available in natural HDPE bottles of 100.

7 WARNINGS AND PRECAUTIONS

Endocrine and Metabolism

The prolonged use of H_2-receptor antagonists may impair the absorption of protein-bound Vitamin B12 and may contribute to the development of cyanocobalamin (vitamin B12) deficiency.

Gastrointestinal

Where gastric ulcer is suspected the possibility of malignancy should be excluded before therapy with AXID is instituted.

Hepatic/Biliary/Pancreatic

Nizatidine is partially metabolized in the liver; however, in patients with mild to moderate hepatic dysfunction, disposition of nizatidine is similar to that of normal subjects.

Monitoring and Laboratory Tests

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

Renal

As nizatidine is excreted via the kidney, dosage should be adjusted in patients with moderately or severely impaired renal function (see 4 DOSAGE AND ADMINISTRATION and 10 CLINICAL PHARMACOLOGY, 10.3 Pharmacokinetics, Elimination).

7.1 Special Populations

7.1.1 Pregnant Women

The safety of nizatidine during pregnancy has not been established. Reproduction studies performed in rats and rabbits at doses up to 300 times the human dose have revealed no evidence of impaired fertility or teratogenicity. If the administration of AXID is considered to be necessary, its use requires that the potential benefits be weighed against possible hazards to the patient and to the fetus.

7.1.2 Breast-feeding

Nizatidine is secreted in human breast milk in proportion to maternal plasma concentrations (<0.1%); therefore, AXID should not be used in lactating women except when the anticipated benefits clearly outweigh the potential risks to the infant. Caution should be exercised when AXID is administered to nursing mothers.

7.1.3 Pediatrics

Pediatrics (under 18 years of age): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7.1.4 Geriatrics

Geriatrics (over 65 years of age)*:* 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 is not an important factor in determining the disposition of nizatidine. However elderly patients may have reduced renal function (see 4 DOSAGE AND ADMINISTRATION and 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Elimination).

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The following common adverse events were reported by patients taking nizatidine in clinical trials: sweating, urticaria and somnolence.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

Worldwide, controlled clinical trials of nizatidine included over 6,000 patients given nizatidine in studies of varying durations. Placebo-controlled trials in the United States and Canada included over 2,600 patients given nizatidine and over 1,700 given placebo. Among the adverse events in these placebo-controlled trials, anemia (0.2% vs 0%) and urticaria (0.5% vs 0.1%) were significantly more common in the nizatidine group.

Table 2 lists adverse events that occurred at a frequency of 1% or more among nizatidine-treated patients who participated in placebo-controlled trials in the United States and Canada.

Table 2 Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled Clinical Trials in the United States and Canada

Body System/ Adverse Event*	Nizatidine n = 2,694 (%)	Placebo n = 1,729 (%)
Body as a whole		
Headache	16.6	15.6
Abdominal Pain	7.5	12.5
Pain	4.2	3.8
Asthenia	3.1	2.9
Back Pain	2.4	2.6
Chest Pain	2.3	2.1
Infection	1.7	1.1
Fever	1.6	2.3
Surgical Procedure	1.4	1.5
Injury, accident	1.2	0.9
Digestive		
Diarrhea	7.2	6.9
Nausea	5.4	7.4
Flatulence	4.9	5.4
Vomiting	3.6	5.6
Dyspepsia	3.6	4.4
Constipation	2.5	3.8
Dry mouth	1.4	1.3
Nausea and Vomiting	1.2	1.9
Anorexia	1.2	1.6
Gastrointestinal Disorder	1.1	1.2
Tooth disorder	1.0	0.8
Musculoskeletal		
Myalgia	1.7	1.5
Nervous		
Dizziness	4.6	3.8

Body System/ Adverse Event*	Nizatidine n = 2,694 (%)	Placebo n = 1,729 (%)
Insomnia	2.7	3.4
Abnormal dreams	1.9	1.9
Somnolence	1.9	1.6
Anxiety	1.6	1.4
Nervousness	1.1	0.8
Respiratory		
Rhinitis	9.8	9.6
Pharyngitis	3.3	3.1
Sinusitis	2.4	2.1
Cough, increased	2.0	2.0
Skin and Appendages		
Rash	1.9	2.1
Pruritus	1.7	1.3
Special Senses		
Amblyopia	1.0	0.9

*Events reported by at least 1% of nizatidine-treated patients are included.

8.3 Less Common Clinical Trial Adverse Reactions

A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Body as a Whole: Serum sickness-like reactions have occurred rarely in conjunction with nizatidine use.

Cardiovascular: In clinical pharmacology studies, short episodes of asymptomatic ventricular tachycardia occurred in 2 individuals administered nizatidine and in 3 untreated subjects.

Central Nervous System: 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 gynecomastia occurred.

Genitourinary: Reports of impotence have occurred.

Hematologic: Anemia was reported significantly more frequently in nizatidine- than in

placebo-treated patients. Fatal thrombocytopenia was reported in a patient who was treated with nizatidine and another H_2-receptor antagonist. On previous occasions, this patient had experienced thrombocytopenia while taking other drugs. Rare cases of thrombocytopenic purpura have been reported.

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. Since market introduction, hepatitis and jaundice have been reported. Rare cases of cholestatic or mixed hepatocellular and cholestatic injury with jaundice have been reported with reversal of the abnormalities after discontinuation of nizatidine.

Hypersensitivity: As with other H_2-receptor antagonists, rare cases of anaphylaxis following administration of nizatidine have been reported. Rare episodes of hypersensitivity reactions (e.g., bronchospasm, laryngeal edema, rash, and eosinophilia) have been reported. Because cross sensitivity in this class of compounds has been observed, H_2-receptor antagonist should not be administered to individuals with a history of previous hypersensitivity to these agents.

Integumental: Sweating and urticaria were reported significantly more frequently in nizatidine- than in placebo-treated patients. Rash and exfoliative dermatitis were also reported. Vasculitis has been reported rarely.

Other: Hyperuricemia unassociated with gout or nephrolithiasis was reported. Eosinophilia, fever, and nausea related to nizatidine administration have been reported.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

No interactions have been observed between nizatidine and:

- theophylline
- chlordiazepoxide
- lorazepam
- lidocaine
- phenytoin
- warfarin
- aminophylline
- diazepam
- metoprolol

Nizatidine does not inhibit the cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur.

Nizatidine may interact with the use of high doses of aspirin.

9.4 Drug-Drug Interactions

In patients given very high doses (3,900 mg) of ASA daily, increases in serum salicylate levels were seen when nizatidine, 150 mg b.i.d., was administered concurrently.

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Absorption of nizatidine is unaffected by food timing (see 10.3 CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption).

Interactions with specific foods have not been studied.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

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

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Nizatidine is a competitive, reversible inhibitor of the histamine H_2-receptor of gastric-acid secreting cells. Nizatidine is not an anticholinergic agent. It inhibits nocturnal gastric-acid secretion as well as gastric-acid secretion stimulated by food, caffeine, betazole and pentagastrin. Pepsin output is reduced in proportion to the reduced volume of gastric secretions. Nizatidine has little or no effect on basal serum gastrin or food induced hypergastrinemia.

In animal studies, nizatidine was a competitive, reversible, selective antagonist of the histamine H_2 receptors of the rat uterus and the oxyntic cells of the dog stomach. In the conscious dog with a Heidenhain pouch, nizatidine given orally or intravenously antagonized gastric acid secretion induced by histamine, gastrin and methacholine. It was 5 to 10 times more active than cimetidine in this respect.

10.2 Pharmacodynamics

Gastric acid suppression correlates directly with nizatidine doses from 75 to 350 mg. Oral doses of 100 mg or 1.3 mg/kg suppressed gastric acid secretion in sham fed volunteers for 3 hours after the dose. The duration of acid suppression directly correlates with the nizatidine dose. 300 mg nizatidine suppressed acid secretion almost entirely early in the day, and the suppression persisted about 10 hours. Nocturnal acid was suppressed for 10 to 12 hours after 300 mg nizatidine.

Nizatidine was well absorbed from all segments of the dog's small intestine; the ratio of ED_{50} P.O. to ED_{50} I.V. for inhibition of maximal response to histamine was 2.2. Identical molar doses of nizatidine given I.V., I.M., or S.C. were equal in peak effect against histamine-induced gastric acid secretion. Nizatidine was more active and exhibited a longer duration of action than cimetidine on food-induced gastric secretion in the dog.

At equi-potent doses of cimetidine and nizatidine, both the binding affinity of nizatidine for the histamine H_2 receptors of the gastric mucosa of the bullfrog and the duration of inhibition of histamine-stimulated acid secretion were significantly greater than those of cimetidine.

The correlations between peak inhibition of histamine-induced acid secretion and log-dose of nizatidine (R = 0.93), and peak plasma concentration and log-dose of nizatidine (R = 0.88) were highly significant.

Dogs receiving nizatidine at oral doses of 5 μmol/kg twice daily did not develop tolerance to the antisecretory effects in a 15-day study.

The N-desmethylated metabolite of nizatidine had 61% of the activity of nizatidine on maximal gastric response to histamine. The sulfoxide derivative of nizatidine was inactive.

On a molar basis, the cytoprotective effect of nizatidine on gastric lesions induced by pyloric ligation and aminoguanidine, or HCl and ASA was at least 5 times greater than cimetidine.

Nizatidine does not stimulate receptors in isolated smooth and cardiac muscle preparations of the guinea pig and rat. In anesthetized dogs given I.V. nizatidine, heart rate and cardiac output were slightly decreased, while stroke volume was slightly increased. Other cardiovascular and respiratory parameters were not altered. Nizatidine given orally to rats is devoid of effects on renal function as estimated by changes in the excretion of urine, electrolytes, and creatinine. Nizatidine given orally or I.P. had no effect on extensor convulsions induced by pentylenetetrazole or electric shock, acetic acid-induced writhing, or hexobarbital sleeping time in mice.

Nizatidine has no competitive binding to high affinity, low capacity androgen receptor sites. Nizatidine as tested in rats does not have anti-androgen activity, nor an effect on plasma concentrations of androgen, nor any significant effect on prolactin release.

10.3 Pharmacokinetics

Absorption

Nizatidine is absorbed rapidly after oral administration. Peak plasma concentrations occur from 0.5 to 3 hours after the dose. Absorption is unaffected by food or propantheline. The absolute oral bioavailability of nizatidine is 70.9% $\pm$ 6.4. Approximately 35% of nizatidine is bound to plasma protein, primarily α-1-glyco-protein. This binding is not influenced by other drugs such as warfarin, diazepam, acetaminophen, propranolol, or phenobarbital.

Antacids consisting of aluminum and magnesium hydroxides with simethicone decrease absorption of nizatidine by about 10%. With food the AUC and C_{max} increase by approximately 10%.

Treatment for up to 2 weeks with nizatidine 600 mg daily did not influence the serum concentrations of gonadotropins, prolactin, growth hormone, antidiuretic hormone, cortisol, triiodothyronine, thyroxin, testosterone, 5-α-dihydro-testosterone, androstenedione or estradiol.

Animal pharmacokinetic studies using radiocarbon-labelled drug have shown nizatidine to be rapidly absorbed from the gastrointestinal tracts of fasted rats and dogs. Maximum plasma concentrations of nizatidine were achieved within 30 minutes of oral administration of 10 mg/kg to rats and 5 mg/kg to dogs. The apparent plasma half-life of nizatidine in these species was 1.1 and 1.5 hours, respectively, while the half-life of total radiocarbon, representing unaltered nizatidine and metabolites was 3.4 and 2.8 hours, respectively. Food hindered nizatidine absorption in the rat. The half-life of nizatidine in the fed animal was 2.6 hours. The absolute bioavailability of nizatidine in the dog for a 5 mg/kg dose was 82%.

Distribution

Radiocarbon levels in male rats after oral administration of a single dose of 10 mg/kg of ^{14}C-nizatidine, in all tissues with the exception of liver and kidney (organs involved directly in metabolism and elimination) were comparable to levels found in the plasma. The half-life of radiocarbon in most tissues was not significantly different than that achieved in the plasma.

Metabolism

Nizatidine has no significant effect on the liver weight or cytochrome P-450 content in rats. Nizatidine weakly inhibits N-demethylation of ethylmorphine by hepatic microsomes by means of non-competitive inhibition kinetics. Cimetidine is a potent inhibitor characterized by mixed inhibition kinetics.

Elimination

In humans, approximately 90% of an oral dose of nizatidine is excreted in the urine within 12 hours. The elimination half-life is one to two hours and the systemic plasma clearance is about 50 L/hour. The volume of distribution is 0.8 to 1.5 L/kg. About 60% of an oral dose and about 77% of an I.V. dose of nizatidine is excreted as unchanged drug.

In animals, nizatidine was excreted by both renal and biliary routes, the former being the major route in the rat and dog. Unaltered nizatidine was the major component in the urine and bile of rats and in the urine of dogs. Minor metabolites eliminated by the rat included N-desmethyl nizatidine, nizatidine sulfoxide and nizatidine N-oxide. The minor metabolites in dog urine were nizatidine N-oxide, nizatidine N-desmethyl and nizatidine sulfoxide.

Since nizatidine is primarily excreted in the urine, renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine. In anephric individuals with creatinine clearance less than 10 mL/min., the half-life is 3.5 to 11 hours and the plasma clearance is 7 to 14 L/hour.

Special Populations and Conditions

- **Geriatrics:** The pharmacokinetic profile for nizatidine in the elderly was not significantly different from the profile in younger normal subjects. However elderly patients may have reduced renal function.
- **Hepatic Insufficiency:** In patients with mild to moderate hepatic dysfunction, disposition of nizatidine is similar to that of normal subjects.
- **Renal Insufficiency:** Renal impairment significantly prolongs the half-life and decreases the clearance of nizatidine**.**

11 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (15°C to 30°C).

Keep out of reach and sight of children. Bring unused and expired prescription drugs to your local pharmacist for proper disposal.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

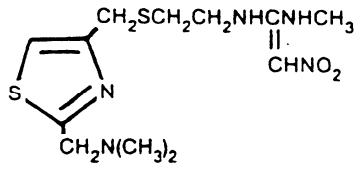
Drug Substance

Proper name: Nizatidine

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

Molecular formula and molecular mass: $C_{12}H_{21}N_5O_2S_2$ / 331.46

Structural formula:



Physicochemical properties: Nizatidine is a lipophobic, off-white to buff crystalline solid.
Melting Point: 30-131.5°C
pKa: Dimethylformamide 66%: 6.25, 8.4; Water: 2.1, 6.8
pH: Aqueous 1% Solution: 9.0

14 CLINICAL TRIALS

The clinical trial data on which the original indication was authorized is not available.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Acute Toxicity

Species	Route	Sex	No. of Animals	Nizatidine LD_{50} (mg/kg)
Mouse	Oral	M	50	1689
		F	50	1630
	I.V.	M	60	236
		F	50	232
	S.C.	M	50	1174
		F	50	1082
Rat	Oral	M	60	2240
		F	50	1653
	I.V.	M	40	301
		F	50	301
	S.C.	M	20	>2000 (LD_0)
		F	20	
Dog	Oral	M	4	>800 (LD_0)
		F	4	
	I.V.	M	2	>75 (LD_0)
		F	2	
	I.M.	M	2	>225(LD_0)
		F	2	
Monkey	Nasogastric	M	2	>1200 (LD_0)
		F	2	
	I.V.	M	2	>200(LD_0)
		F	2	

Signs of toxicity included: vomiting, salivation, vasodilation, ptosis, tremors, hypoactivity, diarrhea, ataxia and lacrimation.

Subacute Toxicity

Mice (5/sex/dose) were maintained on diets containing 0, 0.225, 0.45, 0.9, or 1.8% nizatidine for 14 days. All animals survived. There were no physical signs of toxicity, or toxicologically significant changes in hematologic or serum chemistry parameters. There was a slight increase in liver weight at the 1.8% treatment level.

Mice were maintained for 3 months on diets containing 0, 0.05, 0.3 or 1.5% nizatidine. All mice receiving nizatidine survived. Female mice had slight dose-related decreases in mean

body weight gains. An increase in liver weight at the 1.5% treatment level was seen.

Rats fed nizatidine at doses of 0.225% or 1.0% (ca. 169, or 773 mg/kg/day) for three months had minor toxicological changes including decreased body weight gain, food consumption, and efficiency of food utilization. There was no evidence of adverse effects in rats receiving 0.05% (ca. 38 mg/kg/day) for three months.

Dogs given up to 800 mg/kg/day orally for two weeks experienced vasodilatation, lacrimation, and vomiting. One dog receiving 800 mg/kg/day had an elevated leukocyte count and an increased serum alanine transaminase activity.

Dogs survived oral doses up to 800 mg/kg/day of nizatidine for three months without significant impairment of tissue or organ systems. Treatment-related effects included slight decreases in hemoglobin and associated erythrocytic parameters, decreased hepatic p-nitroanisole O-demethylase activity, and a significant reduction in body weight for one female at the 800 mg/kg/day nizatidine treatment level.

Chronic Toxicity

Nizatidine was given daily to rats (20/sex/dose) for six months at dietary levels of 0, 0.05%, 0.225%, or 1.0% (ca. 0, 30, 136 and 617 mg/kg). Physical signs of toxicity were perineal soiling in females receiving 0.225% and 1.0%, and decreased mean body weight gains for females receiving 0.225% and both sexes receiving 1% nizatidine. Efficiency of food utilization was decreased for rats at the 1% treatment level. Increases occurred in the weights of livers from males receiving 0.225%, and in the livers and kidneys from males and females at the 1% nizatidine treatment level.

Rats were maintained for 1 year at dietary levels of 0, 0.05%, 0.225% and 1.0% nizatidine (ca. 0, 27, 121, and 544 mg/kg/day). The highest dose was approximately 110 times the recommended human dose. The minor toxicological changes that occurred were similar to the three and six-month studies.

Beagle dogs (4/sex/dose) received daily oral doses of 0, 50, 140 or 400 mg/kg/day for one year. The highest dose was 80 times the recommended human dose. Physical signs of toxicity were similar to those seen in previous subchronic studies. Additional signs of toxicity were diarrhea, blood in feces, miosis with or without increased pupillary light reflex, decreased thrombocyte counts, and decreased hepatic microsomal enzyme activity and cytochrome P-450 content

Carcinogenicity

Two-year oral carcinogenicity studies with nizatidine in rats and mice revealed no carcinogenic response at doses up to 2175 mg/kg. These dose levels are equivalent to approximately 800 times the maintenance dose in man.

Genotoxicity

The mutagenicity of nizatidine was evaluated in a battery of *in vitro* and *in vivo* tests utilizing

bacterial mutation (Ames and Modified Ames tests), unscheduled DNA synthesis, sister chromatid exchange (I.P. and P.O. administration), and the mouse lymphoma assay. Nizatidine was found to have no mutagenic effect in each study.

Reproductive and Developmental Toxicology

Adult female Fischer 344 rats (10/dose) received daily dietary doses of 0, 0.05, 0.225, or 1.0% nizatidine (ca. 0, 27, 119, or 506 mg/kg) for a two-week premating period and throughout breeding and gestation. Approximately double these dietary doses were provided during lactation. The females were mated with males from corresponding treatment groups that were assigned to the three-month subacute study. Food consumption and body weights decreased, as did progeny body weights. Coolness, dehydration and stickiness were observed in the progeny of treated dams. Due to the small sample sizes, lack of a dose-responsive relationship and high inter-litter variability, meaningful evaluation of progeny survival data was not possible.

Adult female Wistar rats (10/dose) received daily dietary doses of 0, 0.01, 0.05, 0.225, and 1.0% (ca. 0, 7, 35, 155 and 680 mg/kg) for a two-week premating period. During gestation, approximately 1.3-2 times those doses were administered during lactation. The females were mated with previously untreated males that received treated diets only during the mating period. Parental toxicity was expressed at the 1% treatment level as decreased food consumption and body weights. Progeny body weights were decreased only at the 1% treatment level. Progeny survival was not affected.

A two-generation fertility, perinatal, and postnatal study was conducted with 80 male and 160 female Wistar rats. The dose levels were 0, 0.05, 0.225 and 1.0% (ca. 0, 33, 143 and 648 mg/kg/day). Females of the F0 generation showed decreased food consumption, body weight, and/or body weight gain. F1 animals had slightly decreased body weights and food consumption.

Teratology

Nizatidine was administered by oral gavage to 25 mated Wistar rats per dose level at doses of 0, 50, 275, and 1500 mg/kg/day on gestation days 6-15. Maternal effects were reduced food consumption and net body weight gain. There were no reproductive or fetal effects.

Groups of 20 pregnant Dutch Belted rabbits were given daily oral doses of 0, 50, 275, or 1500 mg/kg on gestation days 6-18. Two females from the 1500 mg/kg/day group died during the study. Loose stools, and/or bloody discharges, decreased body weight gain and decreased food consumption occurred at the 1500 mg/kg/day treatment level. Six animals from the 1500 mg/kg group aborted between gestation days 18 and 26 following anorexia and loss of body weight. The mean percent of live fetuses was decreased at the 1500 mg/kg dose level. Decreased fetal body weights and increased percent of abnormal fetuses attributed to runting were also noted, this indicated fetal growth retardation associated with severe maternal toxicity. There was no evidence of a teratogenic effect as defined as an increase in the incidence of frank structural malformations.

Nizatidine was administered by gavage to mated female New Zealand White rabbits (20 animals/group) at dose levels of 0, 50, 275, and 1000 mg/kg/day on gestation days 6 through 18. Maternal toxicity was indicated by decreased body weight and food consumption and an increased incidence of transient diarrhea or soft stool in the high-dose group. The no-effect level for maternal toxicity was 275 mg/kg/day. Fetal toxicity was indicated by decreased fetal weights, an increased incidence of fetal runts, and a trend toward increased fetal resorptions in the high dose group. The no effect level for developmental toxicity was 275 mg/kg/day. There was no indication of nizatidine-induced teratogenicity.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

AXID

Nizatidine Capsules

Read this carefully before you start taking **AXID** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **AXID**.

What is AXID used for?

AXID is used to treat stomach acid related problems. This includes:

- Healing and pain relief of ulcers (sores) on the lining of the duodenum. The duodenum is the first part of the small intestine.
- Healing and pain relief of sores on the lining of the stomach.
- Healing and pain relief caused by gastro-esophageal reflux disease (GERD). This is a condition where stomach acid backs up into your esophagus (gullet). This can cause pain or discomfort known as indigestion, acid reflux or heartburn.
- Preventing sores on the lining of the duodenum from coming back.

How does AXID work?

AXID belongs to a group of medicines called H_2-receptor antagonists (anti-ulcer medicines). It works by reducing the amount of acid in your stomach.

What are the ingredients in AXID?

Medicinal ingredients: Nizatidine

Non-medicinal ingredients:
150 mg capsules: Corn starch, magnesium stearate, pregelatinized starch and silicon fluid.

The printed capsule shells also contain benzyl alcohol, butylparaben, calcium disodium edetate, carboxy-methylcellulose sodium, gelatin, iron oxide black, iron oxide yellow, methylparaben, potassium hydroxide, propylparaben, shellac, sodium lauryl sulfate, sodium propionate and titanium dioxide.

300 mg capsules: Corn starch, carboxymethylcellulose sodium, pregelatinized starch, povidone, silicon fluid and talc.

The printed capsule shells also contain benzyl alcohol, butylparaben, calcium disodium edetate, gelatin, iron oxide black, iron oxide red, iron oxide yellow, methylparaben, potassium

hydroxide, propylparaben, shellac, sodium lauryl sulfate, sodium propionate and titanium dioxide.

AXID comes in the following dosage forms:

Capsules 150 mg and 300 mg

Do not use AXID if:

- you are allergic to nizatidine or to any of the other ingredients in AXID. (See "What are the ingredients in AXID?").
- you are allergic to any drug in the group of medicines called H_2-receptor antagonists

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take AXID. Talk about any health conditions or problems you may have, including if you:

- have kidney problems.
- have liver problems.
- are pregnant or plan to become pregnant.
- are breast-feeding or plan to breast-feed. AXID passes in breast milk.

Other warnings you should know about:

- Long-term use of AXID may lead to Vitamin B12 deficiency.
- AXID can cause abnormal urine test results (false-positive results) for a liver compound called urobilinogen.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with AXID:

- Aspirin: Acetylsalicylic Acid (ASA), used to treat pain and fever

How to take AXID:

- Use AXID exactly as directed by your healthcare professional.
- Take AXID with a full glass of water.
- Antacids may be used together with AXID if needed.
- Do not share your medicine.

Usual dose:

Adults

- **For stomach or duodenal ulcers:** One 300 mg capsule or two 150 mg capsules once daily at bedtime. Alternatively, 150 mg twice daily may be used. Healing occurs within 4 weeks in most cases of duodenal ulcer. If your ulcer has not fully healed after 4 weeks, your doctor may treat you for a further 4 weeks.
- **Maintenance therapy in duodenal ulcer:** One 150 mg capsule once daily at bedtime for 6 - 12 months depending on the severity of the condition.
- **Gastroesophageal Reflux Disease**: One 150 mg capsule twice daily for the treatment of indigestion, acid reflux and heartburn.

Overdose:

If you think you, or a person you are caring for, have taken too much AXID, contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

Take the missed dose as soon as you remember. Skip the missed dose if it is almost time for your next scheduled dose. Do not take extra medicine to make up the missed dose.

What are possible side effects from using AXID?

These are not all the possible side effects you may have when taking AXID. If you experience any side effects not listed here, tell your healthcare professional.

Side effects may include:

- sweating
- sleepiness
- headache
- stomach pain
- feeling weak or tired
- pain in your whole body
- back pain
- chest pain
- diarrhea
- vomiting
- passing gas more than usual
- constipation
- indigestion
- nausea (feeling sick)
- heartburn

- insomnia (difficulty falling asleep)
- feeling anxious or nervous
- runny or stuffed nose
- sore throat
- increased coughing
- dizziness
- hives (urticaria)
- rash
- fever
- lazy eye
- unusual tiredness, shortness of breath when exercising
- flaking or peeling of the skin
- joint pain, aching muscles, muscle tenderness or weakness not caused by exercise
- if you are a man, breast enlargement or an inability to get or maintain an erection
- confusion

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
RARE			
Allergic Reaction: difficulty swallowing or breathing, wheezing; drop in blood pressure; feeling sick to your stomach and throwing up; hives or rash; swelling of the face, lips, tongue or throat.			✓
Liver Disorder: yellowing of the skin or eyes, dark urine and pale stools, abdominal pain, nausea, vomiting, itching		✓	
Anemia (decreased number of red blood cells): fatigue, loss of energy, irregular heartbeats, pale complexion, shortness of breath, weakness		✓	
Thrombocytopenia (low blood platelets): bruising or bleeding for longer than usual if you hurt yourself, fatigue and weakness		✓	
Eosinophilia (increased numbers of certain white blood cells): abdominal pain, rash, weight loss, wheezing.		✓	
Vasculitis (narrowing or blockage of the blood vessels): general feeling of being unwell, fever, tiredness, weight loss		✓	
Frequent infections such as fever, severe chills, sore throat or mouth ulcers		✓	
Hyperuricemia (high uric acid levels in the blood): severe pain and swelling in the joints, kidney stones			✓

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store at room temperature (15°C to 30°C).

Keep out of reach and sight of children.

If you want more information about AXID:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html; the manufacturer's website www.pendopharm.com, or by calling 1-888-550-6060.

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