Usual Adult Dose:
See accompanying literature for dosage.

Keep tightly closed.

Store at controlled room temperature 20° to 25°C (68° to 77°F) [see USP].

Manufactured for:
Reliant Pharmaceuticals, Inc.
Liberty Corner, NJ 07938
by:
Patheon Pharmaceuticals Inc.
Cincinnati, OH 45237
Axid, 150 mg h.s.

- The absolute oral bioavailability of nizatidine is unaffected by concomitant administration of antacids, sucralfate, or food.

- In a multicenter, double-blind, placebo-controlled study conducted with an H2-receptor antagonist at the dose of 150 mg h.s., Axid significantly inhibited gastric acid secretion stimulated by caffeine and pentagastrin. However, studies conducted in lactating women have not been established.

- Treatment with a reduced dose of Axid has been shown to be not inferior to standard therapy.

- Effect of Oral Axid on Gastric Acid Secretion

<table>
<thead>
<tr>
<th>Time After % Inhibition of Gastric Acid</th>
<th>20-50</th>
<th>75</th>
<th>100</th>
<th>150</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-50</td>
<td>64%</td>
<td>92%</td>
<td>153%</td>
<td>175%</td>
<td>187%</td>
</tr>
<tr>
<td>75</td>
<td>112%</td>
<td>152%</td>
<td>172%</td>
<td>182%</td>
<td>187%</td>
</tr>
<tr>
<td>100</td>
<td>112%</td>
<td>152%</td>
<td>172%</td>
<td>182%</td>
<td>187%</td>
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<td>150</td>
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<td>300</td>
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<td>152%</td>
<td>172%</td>
<td>182%</td>
<td>187%</td>
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</tbody>
</table>

- The structural formula is as follows:

```
\text{H} \quad \text{C} \quad \text{S} \\
\text{CH}_3 \quad \text{N} \quad \text{CH}_2 \quad \text{N} \quad \text{CH}_3
```

- Caffeine Up to 3 73 85 96
- Pentagastrin Up to 6 25 64 67

<table>
<thead>
<tr>
<th>Percentage of Ulcers Recurring by 3, 6, and 12 Months in Active Duodenal Ulcer</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients, n (%)</td>
<td>29/88 (33%)</td>
<td>98 13/92 (14%)</td>
<td>39/79 (49%)</td>
</tr>
</tbody>
</table>

- Niz 300 mg h.s. 52/153 (34%) 0.342

- The data suggest that Axid is effective in the treatment of active duodenal ulcer and is superior to historical placebo control rates.

- Absolute bioavailability (214F400)

- Emphasis has been placed on Axid's effectiveness in healing erosive and ulcerative esophagitis. Axid also significantly inhibited gastric acid secretion stimulated by caffeine up to 64%.
### DOSAGE AND ADMINISTRATION

**Active Duodenal Ulcer**

- For treatment, the recommended oral dosage is 150 mg once daily at bedtime.
- For follow-up maintenance therapy, the recommended oral dosage is 150 mg twice daily.

**Active Benign Gastric Ulcer**

- The recommended oral dosage is 300 mg given either as 150 mg twice daily or 300 mg once daily at bedtime. Prior to treatment, care should be taken to exclude the possibility of malignant gastric ulceration.

**Gastroesophageal Reflux Disease (GERD)**

- The recommended oral dosage is 150 mg twice daily.

**Dosage Adjustment for Patients With Moderate to Severe Renal Impairment**

- The dosage for adults is 150 mg once daily at bedtime.
- For patients with severe renal impairment (CrCl 10 to 29 mL/minute), the dosage should be 150 mg once daily at bedtime.

### DOSAGE FOR KIDNEYS AND LIVER

- For patients with severe renal impairment, the dosage should be 150 mg once daily at bedtime.
- For patients with moderate renal impairment (CrCl 30 to 59 mL/minute), the dosage should be 150 mg once daily at bedtime.

### DOSAGE FOR PEDIATRIC PATIENTS

- The dosage for children is 0.5 to 1 mg/kg body weight once daily at bedtime.

### DOSAGE FOR PULVULES

- The 300-mg Pulvules are imprinted with “300” on the opaque brown body, using black ink. They are available as follows:
  - Nizatidine (N=2,694)
  - Placebo (N=1,729)

### DOSAGE FOR INTRAVENOUS ADMINISTRATION

- Intravenous median lethal doses in the rat and mouse were 800 mg/kg in dogs and of 1,200 mg/kg in monkeys were not lethal.

### CONTRAINDICATIONS

- Nizatidine is contraindicated in patients with known hypersensitivity to it or to any of its components.

### WARNINGS

- Nizatidine increases gastric pH and delays gastric emptying.

### ADVERSE REACTIONS

#### BODY AS A WHOLE

- Fatigue, asthenia, and fever were significantly more common in the nizatidine group.

#### CARDIOVASCULAR

- Hypertension and/or tachycardia were significantly more common in the nizatidine group.

#### DIGESTIVE

- Nausea, vomiting, and diarrhea were significantly more common in the nizatidine group.

#### HEMATOLOGIC

- Anemia was reported significantly more frequently in the nizatidine group.

#### INTEGUMENTAL

- Dermatitis, rash, pruritus, and urticaria were significantly more common in the nizatidine group.

#### NEUROLOGIC

- Nervousness, anxiety, and abnormal dreams were significantly more common in the nizatidine group.

#### RESPIRATORY

- Dyspnea and cough were significantly more common in the nizatidine group.

### PRECAUTIONS

- Nizatidine is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

### DOSAGE FORMS

- Axid® Pulvules® are available in:
  - 300-mg Pulvules
  - 150-mg Pulvules

### OVERDOSAGE

- In managing overdose, consider the possibility of multiple drug overdoses, interaction among drugs, and unusual drug kinetics in your patient.
Nizatidine has the empirical formula C_{12}H_{21}N_{5}O_{2}S_{2} representing a molecular weight of 331.47. It is an off-white protein, mainly to α-glycosidase. Warfarin, diazepam, acetaminophen, prednisone, phenobarbital, and propranolol did not affect plasma protein binding of nizatidine in vitro. Clinical Trials—1. Active Duodenal Ulcer: In multicenter, double-blind, placebo-controlled studies in the United States, endoscopically diagnosed duodenal ulcers healed more rapidly following administration of Axid, 300 mg h.s. or 150 mg b.i.d., than with placebo (Table 2). Lower doses, such as 100 mg h.s., had slightly lower efficacy.

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<tr>
<th>Time After Dose (h)</th>
<th>% Inhibition of Gastric Acid Output by Dose</th>
<th>20-20</th>
<th>75</th>
<th>100</th>
<th>150</th>
<th>300</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nocturnal</td>
<td>Up to 10</td>
<td>57</td>
<td>73</td>
<td>90</td>
<td>90</td>
<td>90</td>
</tr>
<tr>
<td>Betazole</td>
<td>Up to 3</td>
<td>93</td>
<td>100</td>
<td>99</td>
<td>99</td>
<td>99</td>
</tr>
<tr>
<td>Pentagastrin</td>
<td>Up to 6</td>
<td>25</td>
<td>64</td>
<td>67</td>
<td>67</td>
<td>67</td>
</tr>
<tr>
<td>Meal</td>
<td>Up to 4</td>
<td>41</td>
<td>64</td>
<td>98</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Up to 3</td>
<td>72</td>
<td>85</td>
<td>98</td>
<td>98</td>
<td>98</td>
</tr>
</tbody>
</table>

2. Effects on Other Gastrointestinal Secretions—Pepsin:

Oral administration of 75 to 300 mg of Axid did not affect pepsin activity in gastric secretions. Total pepsin output was reduced in proportion to the reduced volume of gastric secretions.

Table 1—Effect of Oral Axid on Gastric Acid Secretion

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In humans, 7% of an oral dose is metabolized as N2-monodesmethylated 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).

Axid® (nizatidine) Capsules, USP

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. No more than 6% of an administered dose is eliminated in the feces.

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 Axid should be adjusted to prevent the severity of dysfunction (see Dosage and Administration).

Axid is indicated for up to 8 weeks for the treatment of active benign gastric ulcer. Before initiating therapy, care should be taken to exclude the possibility of malignant gastric ulceration.

Contraindication: Axid is contraindicated in patients with known hypersensitivity to the drug. Because cross sensitivity in this class of compounds has been observed, H₂-receptor antagonists, including Axid, should not be administered to patients with a history of hypersensitivity to other H₂-receptor antagonists.

Precautions: General—1. Symptomatic response to nizatidine therapy does not preclude the presence of gastric malignancy. 2. Because nizatidine is excreted primarily by the kidney, dosage should be reduced in patients with moderate to severe renal insufficiency (see Dosage and Administration).

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

Axid is indicated for maintenance therapy for duodenal ulcer patients who have responded to 1 week of administration of Axid 300 mg h.s. after evening meals. The benefit of Axid maintenance therapy has not been demonstrated for periods longer than 1 year.

Axid is indicated for up to 12 weeks for the treatment of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.

Axid is indicated for up to 8 weeks for the treatment of active benign gastric ulcer. Before initiating therapy, care should be taken to exclude the possibility of malignant gastric ulceration.

Drug Interactions—No interactions have been observed between Axid and theophylline, chloridazepoxide, lorazepam, lidocaine, phenytoin, and warfarin. Axid does not inhibit cytochrome P-450-linked drug-metabolizing enzyme system; therefore, drug interactions mediated by inhibition of hepatic metabolism are not expected to occur. In patients given very high doses (3,900 mg) of aspirin daily, increases in serum salicylate levels were seen in patients not taking Axid for 1 week. The pharmacokinetics of nizatidine are similar to those in normal subjects.

More than 90% of an oral dose of nizatidine is 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).

Carcinogenesis, Mutagenesis, Impairment of Fertility—A 2-year oral carcinogenicity study in rats with doses as high as 5,000 mg/kg (about the median human dose of 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, but no evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo. Female mice given the high dose of Axid (2,000 mg/kg/day, about 330 times the human dose) showed markedly statistically significant increases in hepatic carcinoma and hepatic nodular hyperplasia with no numerical increase seen in any of the other dose groups, including the moderate (about the median human dose of therapeutic dose) and no evidence of a carcinogenic effect in rats, male and female mice, and female rats (given up to 360 mg/kg/day, about 60 times the human dose), and a negative mutagenicity battery test are not consistent with evidence of a carcinogenic effect for Axid.

Axid 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, evidence of a carcinogenic effect in male mice, although hyperplastic nodules of the liver were increased in the high-dose males as compared with placebo.

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.
to 1500 mg/kg/day (9000 mg/m²/day). 40.5 times the recommended human dose based on body surface area) and in pregnant rabbits at doses up to 275 mg/kg/day (3245 mg/m²/day, 14.6 times the recommended human dose based on body surface area) have revealed no evidence of teratogenic or embryotoxic effects. A variety of less common events were also reported; it was not possible to determine whether these were caused by nizatidine.

Hepato—Hepatocholangitis: reported. Vasculitis has been reported rarely. 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.

How Supplied: Axid® Pulvules® are available in:

- 150 mg Pulvules: white or almost white, flat, smooth, oval tablets imprinted with “150 mg” and “AXID” on the face of the tablet, and with the number “30” on the back
- 300 mg Pulvules: white or almost white, flat, smooth, oval tablets imprinted with “300 mg” and “AXID” on the face of the tablet, and with the number “30” on the back

How Supplied: The 150-mg Pulvules are imprinted “150” on the opaque dark yellow cap and “AXID” and “Reliant” on the opaque dark yellow body, using black ink. They are available as follows:

- Bottles of 30 NDC 65726-145-10
- Bottles of 60 NDC 65726-144-15

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