HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use PROTONIX safely and effectively. See full prescribing information for PROTONIX.

PROTONIX (pantoprazole sodium) delayed-release tablets

PROTONIX (pantoprazole sodium) for delayed-release oral suspension

Initial U.S. approval: 2000

RECENT MAJOR CHANGES

Indications and Usage, Pediatric (1)	11/2009
Dosage and Administration, Pediatric (2)	11/2009
Contraindications (4)	11/2009
Warnings and Precautions, Bone Fracture (5.4)	0x/2010

INDICATIONS AND USAGE

PROTONIX is a proton pump inhibitor indicated for the following:

- Short-Term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD) (1.1)
- Maintenance of Healing of Erosive Esophagitis (1.2)
- Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (1.3)

DOSAGE AND ADMINISTRATION

Indication	Dose	Frequency
Short-Term Treatment of Erosive Esophagitis Associated With GERD (2.1)		
Adults	40 mg	Once Daily for up to 8 wks
Children (5 years and older)		
≥ 15 kg to < 40 kg	20 mg	Once Daily for up to 8 wks
≥ 40 kg	40 mg	
Maintenance of Healing of Erosive Esophagitis (2.1)		
Adults	40 mg	Once Daily
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome (2.1)		
Adults	40 mg	Twice Daily

See full prescribing information for administration instructions

DOSAGE FORMS AND STRENGTHS

- Delayed-Release Tablets, 20 mg and 40 mg (3)
- For Delayed-Release Oral Suspension, 40 mg (3)

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation or to substituted benzimidazoles (4)

WARNINGS AND PRECAUTIONS

- Symptomatic response does not preclude presence of gastric malignancy (5.1)
- Atrophic gastritis has been noted with long-term therapy (5.2)
- Bone Fracture
  Long-term and multiple daily dose PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine. (5)

ADVERSE REACTIONS

The most frequently occurring adverse reactions are as follows:

- For adult use (>2%) are headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia. (6)
- For pediatric use (>4%) are URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Wyeth Pharmaceuticals Inc. at 1-800-934-5556 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

DRUG INTERACTIONS

- Do not co-administer with atazanavir or nelfinavir (7.1)
- Concomitant warfarin use may require monitoring (7.2)
- May interfere with the absorption of drugs where gastric pH is important for bioavailability (7.3)
- May produce false-positive urine screen for THC (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 12/2009

FULL PRESCRIBING INFORMATION: CONTENTS *

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

PROTONIX For Delayed-Release Oral Suspension and PROTONIX Delayed-Release Tablets are indicated for:

1.1 Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

PROTONIX is indicated in adults and pediatric patients five years of age and older for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered. Safety of treatment beyond 8 weeks in pediatric patients has not been established.

1.2 Maintenance of Healing of Erosive Esophagitis

PROTONIX is indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in adult patients with GERD. Controlled studies did not extend beyond 12 months.

1.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

PROTONIX is indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing Schedule

PROTONIX is supplied as delayed-release granules in packets for preparation of oral suspensions or as delayed-release tablets. The recommended dosages are outlined in Table 1.

Table 1: Recommended Dosing Schedule for PROTONIX

Indication	Dose	Frequency
Short-Term Treatment of Erosive Esophagitis Associated With GERD		
Adults	40 mg	Once daily for up to 8 weeks*
Children (5 years and older)		
≥ 15 kg to < 40 kg	20 mg	Once daily for up to 8 weeks
≥ 40 kg	40 mg	
Maintenance of Healing of Erosive Esophagitis		
Adults	40 mg	Once daily
Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome		
Adults	40 mg	Twice daily**

* For adult patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.
** Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered.

2.2 Administration Instructions

Directions for method of administration for each dosage form are presented in Table 2.

Table 2: Administration Instructions

Formulation	Route	Instructions*
Delayed-Release Tablets	Oral	Swallowed whole, with or without food
For Delayed-Release Oral Suspension	Oral	Administered in 1 teaspoonful of applesauce or apple juice approximately 30 minutes prior to a meal
For Delayed-Release Oral Suspension	Nasogastric tube	See instructions below

* Patients should be cautioned that PROTONIX Delayed-Release Tablets and PROTONIX For Delayed-Release Oral Suspension should not be split, chewed, or crushed.

PROTONIX Delayed-Release Tablets

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. If patients are unable to swallow a 40 mg tablet, two 20 mg tablets may be taken. Concomitant administration of antacids does not affect the absorption of PROTONIX Delayed-Release Tablets.

PROTONIX For Delayed-Release Oral Suspension

PROTONIX For Delayed-Release Oral Suspension should only be administered approximately 30 minutes prior to a meal via oral administration in apple juice or applesauce or nasogastric tube in apple juice only. Because proper pH is necessary for stability, do not administer PROTONIX For Delayed-Release Oral Suspension in liquids other than apple juice, or foods other than applesauce.

Do not divide the 40 mg PROTONIX For Delayed-Release Oral Suspension packet to create a 20 mg dosage for pediatric patients who are unable to take the tablet formulation.

PROTONIX For Delayed-Release Oral Suspension - Oral Administration in Applesauce

- Open packet.
- Sprinkle granules on one teaspoonful of applesauce. DO NOT USE OTHER FOODS OR CRUSH OR CHEW THE GRANULES.
- Take within 10 minutes of preparation.
- Take sips of water to make sure granules are washed down into the stomach. Repeat water sips as necessary.

PROTONIX For Delayed-Release Oral Suspension - Oral Administration in Apple Juice

- Open packet.
- Empty granules into a small cup or teaspoon containing one teaspoon of apple juice.
- Stir for 5 seconds (granules will not dissolve) and swallow immediately.
- To make sure that the entire dose is taken, rinse the container once or twice with apple juice to remove any remaining granules. Swallow immediately.

PROTONIX For Delayed-Release Oral Suspension - Nasogastric (NG) Tube or Gastrostomy Tube Administration

For patients who have a nasogastric tube or gastrostomy tube in place, PROTONIX For Delayed-Release Oral Suspension can be given as follows:

- Remove the plunger from the barrel of a 2 ounce (60 mL) catheter-tip syringe. Discard the plunger.
- Connect the catheter tip of the syringe to a 16 French (or larger) tube.
- Hold the syringe attached to the tubing as high as possible while giving PROTONIX For Delayed-Release Oral Suspension to prevent any bending of the tubing.
- Empty the contents of the packet into the barrel of the syringe.
- Add 10 mL (2 teaspoonfuls) of apple juice and gently tap and/or shake the barrel of the syringe to help rinse the syringe and tube. Repeat at least twice more using the same amount of apple juice (10 mL or 2 teaspoonfuls) each time. No granules should remain in the syringe.

3 DOSAGE FORMS AND STRENGTHS

Delayed-Release Tablets:

- 40 mg, yellow oval biconvex tablets imprinted with PROTONIX (brown ink) on one side
- 20 mg, yellow oval biconvex tablets imprinted with P20 (brown ink) on one side

For Delayed-Release Oral Suspension:

- 40 mg, pale yellowish to dark brownish, enteric-coated granules in a unit dose packet

4 CONTRAINDICATIONS

PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation [*see Description (11)*] or any substituted benzimidazole.

5 WARNINGS AND PRECAUTIONS

5.1 Concurrent Gastric Malignancy

Symptomatic response to therapy with PROTONIX does not preclude the presence of gastric malignancy.

5.2 Atrophic Gastritis

Atrophic gastritis has been noted occasionally in gastric corpus biopsies from patients treated long-term with PROTONIX, particularly in patients who were *H. pylori* positive.

5.3 Cyanocobalamin (Vitamin B-12) Deficiency

Generally, daily treatment with any acid-suppressing medications over a long period of time (e.g., longer than 3 years) may lead to malabsorption of cyanocobalamin (Vitamin B-12) caused by hypo- or achlorhydria. Rare reports of cyanocobalamin deficiency occurring with acid-suppressing therapy have been reported in the literature. This diagnosis should be considered if clinical symptoms consistent with cyanocobalamin deficiency are observed.

5.4 Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines [*see Dosage and Administration (2) and Adverse Reactions (6.2)*].

5.5 Tumorigenicity

Due to the chronic nature of GERD, there may be a potential for prolonged administration of PROTONIX. In long-term rodent studies, pantoprazole was carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these findings to tumor development in humans is unknown [*see Nonclinical Toxicology (13.1)*].

5.6 Interference with Urine Screen for THC

See *Drug Interactions (7.4)*.

6 ADVERSE REACTIONS

The adverse reaction profiles for PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension and PROTONIX (pantoprazole sodium) Delayed-Release Tablets are similar.

6.1 Clinical Trial Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Adults

Safety in nine randomized comparative US clinical trials in patients with GERD included 1,473 patients on oral PROTONIX (20 mg or 40 mg), 299 patients on an H_2-receptor antagonist, 46 patients on another proton pump inhibitor, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table 3.

Table 3: Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%

	PROTONIX (n=1473) %	Comparators (n=345) %	Placebo (n=82) %
Headache	12.2	12.8	8.5
Diarrhea	8.8	9.6	4.9
Nausea	7.0	5.2	9.8
Abdominal pain	6.2	4.1	6.1
Vomiting	4.3	3.5	2.4
Flatulence	3.9	2.9	3.7
Dizziness	3.0	2.9	1.2
Arthralgia	2.8	1.4	1.2

Additional adverse reactions that were reported for PROTONIX in clinical trials with a frequency of ≤ 2% are listed below by body system:

Body as a Whole: allergic reaction, pyrexia, photosensitivity reaction, facial edema

Gastrointestinal: constipation, dry mouth, hepatitis

Hematologic: leukopenia, thrombocytopenia

Metabolic/Nutritional: elevated CK (creatine kinase), generalized edema, elevated triglycerides, liver enzymes elevated

Musculoskeletal: myalgia

Nervous: depression, vertigo

Skin and Appendages: urticaria, rash, pruritus

Special Senses: blurred vision

Pediatric Patients

Safety of PROTONIX in the treatment of Erosive Esophagitis (EE) associated with GERD was evaluated in pediatric patients ages 1 year through 16 years in three clinical trials. Safety trials involved pediatric patients with EE; however, as EE is uncommon in the pediatric population, 249 pediatric patients with endoscopically-proven or symptomatic GERD were also evaluated. All adult adverse reactions to PROTONIX are considered relevant to pediatric patients. In patients ages 1 year through 16 years, the most commonly reported (> 4%) adverse reactions include: URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain.

For safety information in patients less than 1 year of age see *Use in Specific Populations (8.4)*.

Additional adverse reactions that were reported for PROTONIX in pediatric patients in clinical trials with a frequency of ≤ 4% are listed below by body system:

Body as a Whole: allergic reaction, facial edema

Gastrointestinal: constipation, flatulence, nausea

Metabolic/Nutritional: elevated triglycerides, elevated liver enzymes, elevated CK (creatine kinase)

Musculoskeletal: arthralgia, myalgia

Nervous: dizziness, vertigo

Skin and Appendages: urticaria

The following adverse reactions seen in adults in clinical trials were not reported in pediatric patients in clinical trials, but are considered relevant to pediatric patients: photosensitivity reaction, dry mouth, hepatitis, thrombocytopenia, generalized edema, depression, pruritus, leukopenia, and blurred vision.

Zollinger-Ellison Syndrome

In clinical studies of Zollinger-Ellison Syndrome, adverse reactions reported in 35 patients taking PROTONIX 80 mg/day to 240 mg/day for up to 2 years were similar to those reported in adult patients with GERD.

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapproval use of PROTONIX. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

These adverse reactions are listed below by body system:

Immune System Disorders: anaphylaxis (including anaphylactic shock)

Skin and Subcutaneous Tissue Disorders: severe dermatologic reactions (some fatal), including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal), and angioedema (Quincke's edema)

Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis, bone fracture

Renal and Urinary Disorders: interstitial nephritis

Hepatobiliary Disorders: hepatocellular damage leading to jaundice and hepatic failure

Psychiatric Disorders: hallucination, confusion

7 DRUG INTERACTIONS

7.1 Interference with Antiretroviral Therapy

Concomitant use of atazanavir or nelfinavir with proton pump inhibitors is not recommended. Coadministration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance.

7.2 Coumarin Anticoagulants

There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including PROTONIX, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

7.3 Drugs for Which Gastric pH Can Affect Bioavailability

Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

7.4 False Positive Urine Tests for THC

There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving proton pump inhibitors. An alternative confirmatory method should be considered to verify positive results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

Reproduction studies have been performed in rats at oral doses up to 88 times the recommended human dose and in rabbits at oral doses up to 16 times the recommended human dose and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed [*see Nonclinical Toxicology (13.2)*].

8.3 Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. Pantoprazole excretion in human milk has been detected in a study of a single nursing mother after a single 40 mg oral dose. The clinical relevance of this finding is not known. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of PROTONIX for short-term treatment (up to eight weeks) of erosive esophagitis (EE) associated with GERD have been established in pediatric patients 1 year through 16 years of age. Effectiveness for EE has not been demonstrated in patients less than 1 year of age. In addition, for patients less than 5 years of age, there is no appropriate dosage strength in an age-appropriate formulation available. Therefore, PROTONIX is indicated for the short-term treatment of EE associated with GERD for patients 5 years and older. The safety and effectiveness of PROTONIX for pediatric uses other than EE have not been established.

1 year through 16 years of age

Use of PROTONIX in pediatric patients 1 year through 16 years of age for short-term treatment (up to eight weeks) of EE associated with GERD is supported by: a) extrapolation of results from adequate and well-controlled studies that supported the approval of PROTONIX for treatment of EE associated with GERD in adults, and b) safety, effectiveness, and pharmacokinetic studies performed in pediatric patients [*see Clinical Studies (14.1), and Clinical Pharmacology (12.3)*].

Safety of PROTONIX in the treatment of EE associated with GERD in pediatric patients 1 through 16 years of age was evaluated in three multicenter, randomized, double-blind, parallel-treatment studies, involving 249 pediatric patients, including 8 with EE (4 patients ages 1 year

to 5 years and 4 patients 5 years to 11 years). The children ages 1 year to 5 years with endoscopically diagnosed EE (defined as an endoscopic Hetzel-Dent score ≥ 2) were treated once daily for 8 weeks with one of two dose levels of PROTONIX (approximating 0.6 mg/kg or 1.2 mg/kg). All 4 of these patients with EE were healed (Hetzel-Dent score of 0 or 1) at 8 weeks. Because EE is uncommon in the pediatric population, predominantly pediatric patients with endoscopically-proven or symptomatic GERD were also included in these studies. Patients were treated with a range of doses of PROTONIX once daily for 8 weeks. For safety findings see *Adverse Reactions (6.1)*. Because these pediatric trials had no placebo, active comparator, or evidence of a dose response, the trials were inconclusive regarding the clinical benefit of PROTONIX for symptomatic GERD in the pediatric population. The effectiveness of PROTONIX for treating symptomatic GERD in pediatric patients has not been established.

Although the data from the clinical trials support use of PROTONIX for the short-term treatment of EE associated with GERD in pediatric patients 1 year through 5 years, there is no commercially available dosage formulation appropriate for patients less than 5 years of age [*see Dosage and Administration (2)*].

In a population pharmacokinetic analysis, clearance values in the children 1 to 5 years old with endoscopically proven GERD had a median value of 2.4 L/h. Following a 1.2 mg/kg equivalent dose (15 mg for ≤ 12.5 kg and 20 mg for > 12.5 to < 25 kg), the plasma concentrations of pantoprazole were highly variable and the median time to peak plasma concentration was 3 to 6 hours. The estimated AUC for patients 1 to 5 years old was 37% higher than for adults receiving a single 40 mg tablet, with a geometric mean AUC value of 6.8 µg•hr/mL.

Neonates to less than one year of age

PROTONIX was not found to be effective in a multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of 129 pediatric patients 1 through 11 months of age. Patients were enrolled if they had symptomatic GERD based on medical history and had not responded to non-pharmacologic interventions for GERD for two weeks. Patients received PROTONIX daily for four weeks in an open-label phase, then patients were randomized in equal proportion to receive PROTONIX treatment or placebo for the subsequent four weeks in a double-blind manner. Efficacy was assessed by observing the time from randomization to study discontinuation due to symptom worsening during the four-week treatment-withdrawal phase. There was no statistically significant difference between PROTONIX and placebo in the rate of discontinuation.

In this trial, the adverse reactions that were reported more commonly (difference of ≥ 4%) in the treated population compared to the placebo population were elevated CK, otitis media, rhinitis, and laryngitis.

In a population pharmacokinetic analysis, the systemic exposure was higher in patients less than 1 year of age with GERD compared to adults who received a single 40 mg dose (geometric mean AUC was 103% higher in preterm infants and neonates receiving single dose of 2.5 mg of PROTONIX, and 23% higher in infants 1 through 11 months of age receiving a single dose of approximately 1.2 mg/kg). In these patients, the apparent clearance (CL/F) increased with age (median clearance: 0.6 L/hr, range: 0.03 to 3.2 L/hr).

These doses resulted in pharmacodynamic effects on gastric but not esophageal pH. Following once daily dosing of 2.5 mg of PROTONIX in preterm infants and neonates, there was an increase in the mean gastric pH (from 4.3 at baseline to 5.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 60% at baseline to 80% at steady-state). Following once daily dosing of approximately 1.2 mg/kg of PROTONIX in infants 1 through 11 months of age, there was an increase in the mean gastric pH (from 3.1 at baseline to 4.2 at steady-state) and in the mean % time that gastric pH was > 4 (from 32% at baseline to 60% at steady-state). However, no significant changes were observed in mean intraesophageal pH or % time that esophageal pH was < 4 in either age group.

Because PROTONIX was not shown to be effective in the randomized, placebo-controlled study in this age group, the use of PROTONIX for treatment of symptomatic GERD in infants less than 1 year of age is not indicated.

8.5 Geriatric Use

In short-term US clinical trials, erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with PROTONIX were similar to those found in patients under the age of 65. The incidence rates of adverse reactions and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

8.6 Gender

Erosive esophagitis healing rates in the 221 women treated with PROTONIX Delayed-Release Tablets in US clinical trials were similar to those found in men. In the 122 women treated long-term with PROTONIX 40 mg or 20 mg, healing was maintained at a rate similar to that in men. The incidence rates of adverse reactions were also similar for men and women.

8.7 Patients with Hepatic Impairment

Doses higher than 40 mg/day have not been studied in patients with hepatic impairment [*see Clinical Pharmacology (12.3)*].

10 OVERDOSAGE

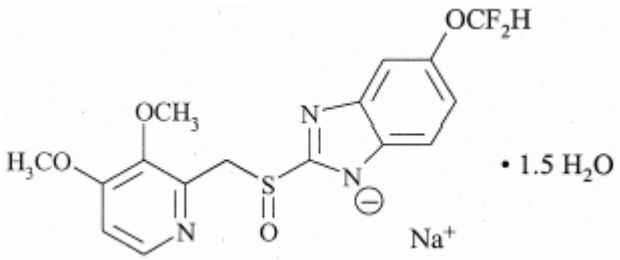
Experience in patients taking very high doses of PROTONIX (> 240 mg) is limited. Spontaneous post-marketing reports of overdose are generally within the known safety profile of PROTONIX.

Pantoprazole is not removed by hemodialysis. In case of overdosage, treatment should be symptomatic and supportive.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg, and 887 mg/kg were lethal to mice, rats, and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

11 DESCRIPTION

The active ingredient in PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension and PROTONIX (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1*H*-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$ x 1.5 H_2O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5 and approximately 220 hours at pH 7.8.

PROTONIX (pantoprazole sodium) is supplied as a for delayed-release oral suspension, available in one strength (40 mg), and as a delayed-release tablet, available in two strengths (20 mg and 40 mg).

Each PROTONIX (pantoprazole sodium) Delayed-Release Tablet contains 45.1 mg or 22.56 mg of pantoprazole sodium sesquihydrate (equivalent to 40 mg or 20 mg pantoprazole, respectively) with the following inactive ingredients: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. PROTONIX Delayed-Release Tablets (40 mg and 20 mg) complies with USP dissolution test 2.

PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension, 40 mg, contains the active ingredient pantoprazole sodium sesquihydrate in the form of enteric-coated granules in unit dose packets. Each unit dose packet contains enteric-coated granules containing 45.1 mg pantoprazole sodium sesquihydrate (equivalent to 40 mg of pantoprazole) with the following inactive ingredients: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+, K^+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion, irrespective of the stimulus. The binding to the (H^+, K^+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested (20 mg to 120 mg).

12.2 Pharmacodynamics

PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension, 40 mg has been shown to be comparable to PROTONIX (pantoprazole sodium) Delayed-Release Tablets in suppressing pentagastrin-stimulated MAO in patients (n = 49) with GERD and a history of EE. In this multicenter, pharmacodynamic crossover study, a 40 mg oral dose of PROTONIX For Delayed-Release Oral Suspension administered in a teaspoonful of applesauce was compared with a 40 mg oral dose of PROTONIX Delayed-Release Tablets after administration of each formulation once daily for 7 days. Both medications were administered thirty minutes before breakfast. Pentagastrin-stimulated (MAO) was assessed from hour 23 to 24 at steady state.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of intravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once-a-day dosing for 7 days, the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies, pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced significantly greater increases in gastric pH than the 20 mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown in Table 4.

Table 4: Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH

	Median pH on day 7			
Time	Placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*#	3.9*#
8 a.m. - 10 p.m. (Daytime)	1.6	3.2*	4.4*#	4.8*#

Table 4: Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH

	Median pH on day 7			
Time	Placebo	20 mg	40 mg	80 mg
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
# Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of PROTONIX for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20, and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8-week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups. Median serum gastrin levels remained within normal limits during maintenance therapy with PROTONIX Delayed-Release Tablets.

In long-term international studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following short-term treatment with PROTONIX, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density, starting after the first year of use, which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery [*see Nonclinical Toxicology (13.1)*].

12.3 Pharmacokinetics

PROTONIX Delayed-Release Tablets are prepared as enteric-coated tablets so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate, and its pharmacokinetics are unaltered with multiple daily dosing. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially, with a terminal elimination half-life of approximately one hour.

In extensive metabolizers with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.5 µg/mL; the time to reach the peak concentration (t_{max}) is 2.5 h, and the mean total area under the plasma concentration versus time curve (AUC) is 4.8 µg•h/mL (range 1.4 to 13.3 µg•h/mL). Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h, and its apparent volume of distribution is 11.0-23.6 L.

A single oral dose of PROTONIX For Delayed-Release Oral Suspension, 40 mg, was shown to be bioequivalent when administered to healthy subjects (N = 22) as granules sprinkled over a teaspoonful of applesauce, as granules mixed with apple juice, or mixed with apple juice followed by administration through a nasogastric tube. The plasma pharmacokinetic parameters from a crossover study in healthy subjects are summarized in Table 5.

Table 5: Pharmacokinetics Parameters (mean ± SD) of PROTONIX For Delayed-Release Oral Suspension at 40 mg

Pharmacokinetic Parameters	Granules in Applesauce	Granules in Apple Juice	Granules in Nasogastric Tube
AUC (µg•hr/mL)	4.0 ± 1.5	4.0 ± 1.5	4.1 ± 1.7
C_{max} (µg/mL)	2.0 ± 0.7	1.9 ± 0.5	2.2 ± 0.7
T_{max} (hr)[a]	2.0	2.5	2.0

[a] Median values are reported for T_{max}.

Absorption

After administration of a single or multiple oral 40 mg doses of PROTONIX Delayed-Release Tablets, the peak plasma concentration of pantoprazole was achieved in approximately 2.5 hours, and C_{max} was 2.5 µg/mL. Pantoprazole undergoes little first-pass metabolism, resulting in an absolute bioavailability of approximately 77%. Pantoprazole absorption is not affected by concomitant administration of antacids.

Administration of PROTONIX Delayed-Release Tablets with food may delay its absorption up to 2 hours or longer; however, the C_{max} and the extent of pantoprazole absorption (AUC) are not altered. Thus, PROTONIX Delayed-Release Tablets may be taken without regard to timing of meals.

Administration of pantoprazole granules, 40 mg, with a high-fat meal delayed median time to peak plasma concentration by 2 hours. With a concomitant high-fat meal, the C_{max} and AUC of

pantoprazole granules, 40 mg, sprinkled on applesauce decreased by 51% and 29%, respectively. Thus, PROTONIX For Delayed-Release Oral Suspension should be taken approximately 30 minutes before a meal.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity.

Elimination

After a single oral or intravenous dose of ^{14}C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine, with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Geriatric

Only slight to moderate increases in pantoprazole AUC (43%) and C_{max} (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole were studied in children less than 16 years of age in four randomized, open-label clinical trials in pediatric patients with presumed/proven GERD. A pediatric granule formulation was studied in children through 5 years of age, and PROTONIX Delayed-Release Tablets were studied in children older than 5 years.

In a population PK analysis, total clearance increased with increasing bodyweight in a non-linear fashion. The total clearance also increased with increasing age only in children under 3 years of age.

Neonate through 5 years of age

See *Use in Specific Populations (8.4)*.

Children and Adolescents 6 through 16 Years of Age

The pharmacokinetics of PROTONIX Delayed-Release Tablets were evaluated in children ages 6 through 16 years with a clinical diagnosis of GERD. The PK parameters following a single oral dose of 20 mg or 40 mg of PROTONIX tablets in children ages 6 through 16 years were highly variable (%CV ranges 40 to 80%). The geometric mean AUC estimated from population PK analysis after a 40 mg PROTONIX tablet in pediatric patients was about 39% and 10% higher respectively in 6 to 11 and 12 to 16 year-old children, compared to that of adults (Table 6).

Table 6: PK Parameters in Children and Adolescents 6 through 16 years with GERD receiving 40 mg PROTONIX Tablets

	6-11 years (n=12)	12-16 years (n=11)
C_{max} (µg/mL)[a]	1.8	1.8
t_{max} (h)[b]	2.0	2.0
AUC (µg•h/mL)[a]	6.9	5.5
CL/F (L/h)[b]	6.6	6.8

[a] Geometric mean values
[b] Median values

Gender

There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is recommended based on gender. In pediatric patients ages 1 through 16 years there were no clinically relevant effects of gender on clearance of pantoprazole, as shown by population pharmacokinetic analysis.

Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment

In patients with mild to severe hepatic impairment (Child-Pugh A to C cirrhosis), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in CYP2C19 poor metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once-daily, multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been studied in hepatically impaired patients.

Drug-Drug Interactions

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6, and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer]), nifedipine, midazolam, and clarithromycin (CYP3A4 substrates), metoprolol (a CYP2D6 substrate), diclofenac, naproxen and piroxicam (CYP2C9 substrates), and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered.

In vivo studies also suggest that pantoprazole does not significantly affect the kinetics of the following drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethinyl estradiol]). Dosage adjustment of these drugs is not necessary when they are coadministered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole.

Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin.

There was also no interaction with concomitantly administered antacids.

There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including PROTONIX, and warfarin concomitantly [*see Drug Interactions (7.2)*].

Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once-daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired.

Other Effects

In a clinical pharmacology study, PROTONIX 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T_3), thyroxine (T_4), thyroid-stimulating hormone (TSH), thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin, and growth hormone.

In a 1-year study of GERD patients treated with PROTONIX 40 mg or 20 mg, there were no changes from baseline in overall levels of T_3, T_4, and TSH.

12.4 Pharmacogenomics

CYP2C19 displays a known genetic polymorphism due to its deficiency in some subpopulations (e.g., approximately 3% of Caucasians and African-Americans and 17% to 23% of Asians are poor metabolizers). Although these subpopulations of pantoprazole poor metabolizers have elimination half-life values of 3.5 to 10.0 hours in adults, they still have minimal accumulation (≤ 23%) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed.

Similar to adults, pediatric patients who have the poor metabolizer genotype of CYP2C19 (CYP2C19 *2/*2) exhibited greater than a 6-fold increase in AUC compared to pediatric extensive (CYP2C19 *1/*1) and intermediate (CYP2C19 *1/*x) metabolizers. Poor metabolizers exhibited approximately 10-fold lower apparent oral clearance compared to extensive metabolizers.

For known pediatric poor metabolizers, a dose reduction should be considered.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50 kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric-fundic ECL cell hyperplasia.

A 26-week p53 +/- transgenic mouse carcinogenicity study was not positive.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

There were no effects on fertility or reproductive performance when pantoprazole was given at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area).

13.2 Animal Toxicology and/or Pharmacology

Studies in neonatal/juvenile and adult rats and dogs were performed. The data from these studies revealed that animals in both age groups respond to pantoprazole in a similar manner. Gastric alterations, including increased stomach weights, increased incidence of eosinophilic chief cells in adult and neonatal/juvenile rats, and atrophy of chief cells in adult rats and in neonatal/juvenile dogs, were observed in the fundic mucosa of stomachs in repeated-dose studies. Decreases in red cell mass parameters, increases in cholesterol and triglycerides, increased liver weight, enzyme induction, and hepatocellular hypertrophy were also seen in repeated-dose studies in rats and/or dogs. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

Reproductive Toxicology Studies

Reproduction studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

14 CLINICAL STUDIES

PROTONIX Delayed-Release Tablets were used in the following clinical trials.

14.1 Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)

Adult Patients

A US multicenter, double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg, or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Hetzel-Dent scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3, and 10% had grade 4. The percentages of patients healed (per protocol, n = 541) in this study are shown in Table 7.

Table 7: Erosive Esophagitis Healing Rates (Per Protocol)

	PROTONIX			Placebo
Week	10 mg daily (n = 153)	20 mg daily (n = 158)	40 mg daily (n = 162)	(n = 68)
4	45.6%[+]	58.4%[+]#	75.0%[+]*	14.3%
8	66.0%[+]	83.5%[+]#	92.6%[+]*	39.7%

[+] ($p < 0.001$) PROTONIX versus placebo
* ($p < 0.05$) versus 10 mg or 20 mg PROTONIX
# ($p < 0.05$) versus 10 mg PROTONIX

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 40 mg and 20 mg PROTONIX treatment groups. The 40 mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20 mg or 10 mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation, starting from the first day of treatment, compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 40 mg and 20 mg once daily were also compared with nizatidine 150 mg twice daily in a US multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n = 212) are shown in Table 8.

Table 8: Erosive Esophagitis Healing Rates (Per Protocol)

	PROTONIX		Nizatidine
Week	20 mg daily (n = 72)	40 mg daily (n = 70)	150 mg twice daily (n = 70)
4	61.4%[+]	64.0%[+]	22.2%
8	79.2%[+]	82.9%[+]	41.4%

[+] ($p < 0.001$) PROTONIX versus nizatidine

Once-daily treatment with PROTONIX 40 mg or 20 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice-daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation, starting on the first day and of daytime heartburn on the second day, compared with those taking nizatidine 150 mg

twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

Pediatric Patients Ages 5 Years through 16 Years

The efficacy of PROTONIX in the treatment of EE associated with GERD in pediatric patients ages 5 years through 16 years is extrapolated from adequate and well-conducted trials in adults, as the pathophysiology is thought to be the same. Four pediatric patients with endoscopically diagnosed EE were studied in multicenter, randomized, double-blind, parallel-treatment trials. Children with endoscopically diagnosed EE (defined as an endoscopic Hetzel-Dent score ≥ 2) were treated once daily for 8 weeks with one of two dose levels of PROTONIX (20 mg or 40 mg). All 4 patients with EE were healed (Hetzel-Dent score of 0 or 1) at 8 weeks.

14.2 Long-Term Maintenance of Healing of Erosive Esophagitis

Two independent, multicenter, randomized, double-blind, comparator-controlled trials of identical design were conducted in adult GERD patients with endoscopically confirmed healed erosive esophagitis to demonstrate efficacy of PROTONIX in long-term maintenance of healing. The two US studies enrolled 386 and 404 patients, respectively, to receive either 10 mg, 20 mg, or 40 mg of PROTONIX Delayed-Release Tablets once daily or 150 mg of ranitidine twice daily. As demonstrated in Table 9, PROTONIX 40 mg and 20 mg were significantly superior to ranitidine at every timepoint with respect to the maintenance of healing. In addition, PROTONIX 40 mg was superior to all other treatments studied.

Table 9: Long-Term Maintenance of Healing of Erosive Gastroesophageal Reflux Disease (GERD Maintenance): Percentage of Patients Who Remained Healed

	PROTONIX 20 mg daily	PROTONIX 40 mg daily	Ranitidine 150 mg twice daily
Study 1	n = 75	n = 74	n = 75
Month 1	91*	99*	68
Month 3	82*	93*#	54
Month 6	76*	90*#	44
Month 12	70*	86*#	35
Study 2	n = 74	n = 88	n = 84
Month 1	89*	92*#	62
Month 3	78*	91*#	47
Month 6	72*	88*#	39
Month 12	72*	83*	37

* ($p < 0.05$ vs. ranitidine)
# ($p < 0.05$ vs. PROTONIX 20 mg)
Note: PROTONIX 10 mg was superior ($p < 0.05$) to ranitidine in Study 2, but not Study 1.

PROTONIX 40 mg was superior to ranitidine in reducing the number of daytime and nighttime heartburn episodes from the first through the twelfth month of treatment. PROTONIX 20 mg,

administered once daily, was also effective in reducing episodes of daytime and nighttime heartburn in one trial, as presented in Table 10.

Table 10: Number of Episodes of Heartburn (mean ± SD)

		PROTONIX 40 mg daily	Ranitidine 150 mg twice daily
Month 1	Daytime	5.1 ± 1.6*	18.3 ± 1.6
	Nighttime	3.9 ± 1.1*	11.9 ± 1.1
Month 12	Daytime	2.9 ± 1.5*	17.5 ± 1.5
	Nighttime	2.5 ± 1.2*	13.8 ± 1.3

* ($p < 0.001$ vs. ranitidine, combined data from the two US studies)

14.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

In a multicenter, open-label trial of 35 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome, with or without multiple endocrine neoplasia-type I, PROTONIX successfully controlled gastric acid secretion. Doses ranging from 80 mg daily to 240 mg daily maintained gastric acid output below 10 mEq/h in patients without prior acid-reducing surgery and below 5 mEq/h in patients with prior acid-reducing surgery.

Doses were initially titrated to the individual patient needs, and adjusted in some patients based on the clinical response with time [*see Dosage and Administration (2)*]. PROTONIX was well tolerated at these dose levels for prolonged periods (greater than 2 years in some patients).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PROTONIX (pantoprazole sodium) Delayed-Release Tablets are supplied as 40 mg yellow, oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side and are available as follows:

- NDC 0008-0841-81, bottles of 90
- NDC 0008-0841-99, carton of 10 Redipak® blister strips of 10 tablets each

PROTONIX (pantoprazole sodium) Delayed-Release Tablets are supplied as 20 mg yellow oval biconvex delayed-release tablets imprinted with P20 (brown ink) on one side and are available as follows:

- NDC 0008-0843-81, bottles of 90

PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension 40 mg contains pale yellowish to dark brownish, enteric-coated granules in a 40 mg unit-dose packet and are available as follows:

- NDC 0008-0844-02, unit-dose carton of 30

Storage

Store PROTONIX For Delayed-Release Oral Suspension and PROTONIX Delayed-Release Tablets at 20° to 25°C (68° to 77°F); excursions permitted to 15° to 30°C (59° to 86°F). [See USP Controlled Room Temperature.]

17 PATIENT COUNSELING INFORMATION

See *FDA-Approved Patient Labeling*.

Patient Counseling

- Caution patients that PROTONIX For Delayed-Release Oral Suspension and PROTONIX Delayed-Release Tablets should not be split, crushed, or chewed.
- PROTONIX oral suspension packet is a fixed dose and cannot be divided to make a smaller dose.
- Tell patients that PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach.
- Let patients know that concomitant administration of antacids does not affect the absorption of PROTONIX Delayed-Release Tablets.
- Advise patients to take PROTONIX For Delayed-Release Oral Suspension approximately 30 minutes before a meal.
- Advise patients that PROTONIX For Delayed-Release Oral Suspension should only be administered in apple juice or applesauce, not in water, other liquids, or foods.

FDA-Approved Patient Labeling

PATIENT INFORMATION

PROTONIX (pro-TAH-nix) (pantoprazole sodium)

For Delayed-Release Oral Suspension and Delayed-Release Tablets

Read the Patient Information that comes with PROTONIX before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or your treatment.

What is PROTONIX?

PROTONIX is a prescription medicine called a proton pump inhibitor (PPI).

PROTONIX is used in adults for:

- Up to 8 weeks for short-term treatment of acid-related damage to the lining of the esophagus (erosive esophagitis) caused by gastroesophageal reflux disease (GERD). If needed, your doctor may prescribe an additional 8 weeks of PROTONIX

- Maintain healing of acid-related damage to the lining of the esophagus and helps prevent return of heartburn symptoms caused by GERD. PROTONIX has not been studied for treatment lasting longer than 1 year
- Treating a rare condition called Zollinger-Ellison Syndrome, where the stomach makes more than the normal amount of acid

PROTONIX is used in children ages 5 years to 16 years old for short-term treatment (for up to 8 weeks) of acid-related damage to the lining of the esophagus (erosive esophagitis) caused by GERD. PROTONIX is not for children under 5 years old.

Who should not take PROTONIX?

Do not take PROTONIX if you are:

- allergic to any of the ingredients in PROTONIX. See the end of this leaflet for a complete list of ingredients in PROTONIX.
- allergic to any proton pump inhibitor (PPI). If you do not know if your medicines are PPIs, please ask your doctor.

What should I tell my doctor before taking PROTONIX?

Before taking PROTONIX, tell your doctor about all your medical conditions, including if you are:

- pregnant, think you may be pregnant, or are planning to become pregnant. It is not known if PROTONIX will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- breastfeeding or planning to breastfeed. PROTONIX may pass into your milk. Talk with your doctor about the best way to feed your baby if you take PROTONIX.

Tell your doctor about all of the medicines you take, including prescription and non-prescription drugs, vitamins and herbal supplements. PROTONIX may affect how other medicines work, and other medicines may affect how PROTONIX works. Especially tell your doctor if you take:

- Warfarin (Coumadin, Athrombin-K, Jantoven, Panwarfin)
- Ketoconazole (Nizoral)
- Atazanavir (Reyataz), Nelfinavir (Viracept)
- Iron supplements
- Ampicillin antibiotics

Ask your doctor if you are not sure if any of your medicines are the kind listed above.

How should I take PROTONIX?

- Take PROTONIX exactly as prescribed by your doctor.
- Do not change your dose or stop PROTONIX without talking to your doctor.
- If you forget to take a dose of PROTONIX, take it as soon as you remember. If it is almost time for your next dose, do not take the missed dose. Take the next dose at your regular time. Do not take two doses to try to make up for a missed dose.
- If you take too much PROTONIX, call your doctor right away.
- See the Patient Instructions for Use at the end of this leaflet for detailed instructions about:
    - how to take PROTONIX tablets
    - how to take PROTONIX For Delayed-Release Oral Suspension
    - how to mix and give PROTONIX For Delayed-Release Oral Suspension through a nasogastric tube or gastric tube.

What are the possible side effects of PROTONIX?

PROTONIX can cause serious side effects including:

- Stomach lining weakening with long-term use
- Vitamin B-12 deficiency
- Serious allergic reactions. Tell your doctor if you get any of the following symptoms with PROTONIX
    - rash
    - face swelling
    - throat tightness
    - difficult breathing

Your doctor may stop PROTONIX if these symptoms happen.

The most common side effects with PROTONIX in adults include:

- Headache
- Diarrhea
- Nausea
- Stomach pain
- Vomiting
- Gas
- Dizziness
- Pain in your joints

The most common side effects with PROTONIX in children include:

- Upper respiratory infection
- Headache
- Fever
- Diarrhea
- Vomiting
- Rash
- Stomach pain

People who are taking multiple daily doses of proton pump inhibitor medicines for a long period of time may have an increased risk of fractures of the hip, wrist or spine.

Tell your doctor about any side effects that bother you or that do not go away.

These are not all the possible side effects with PROTONIX. Talk with your doctor or pharmacist if you have any questions about side effects. Call your doctor for medical advice about side effects. You may report side effects to the FDA at 1-800-FDA-1088.

How should I store PROTONIX?

- Store PROTONIX at room temperature between 59° to 86°F (15° to 30°C).
- Keep PROTONIX and all medicines out of the reach of children.

General Information

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use PROTONIX for a condition for which it was not prescribed. Do not give PROTONIX to other people, even if they have the same symptoms you have. It may harm them.

This Patient Information leaflet provides a summary of the most important information about PROTONIX. For more information, ask your doctor. You can ask your doctor or pharmacist for information that is written for healthcare professionals.

For more information, go to www.wyeth.com or call toll-free 1-800-934-5556.

What are the ingredients in PROTONIX?

Active ingredient: pantoprazole sodium sesquihydrate

Inactive ingredients in PROTONIX Delayed-Release Tablets: calcium stearate, crospovidone, hypromellose, iron oxide, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, sodium lauryl sulfate, titanium dioxide, and triethyl citrate.

Inactive ingredients in PROTONIX For Delayed-Release Oral Suspension, 40 mg: crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose,

polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide.

Patient Instructions for Use

PROTONIX Tablets

- You can take PROTONIX tablets with food or on an empty stomach.
- Swallow PROTONIX tablets whole.
- If you have trouble swallowing a PROTONIX 40 mg tablet, you can take two 20 mg tablets instead.
- Do not split, chew, or crush PROTONIX tablets.

PROTONIX Oral Suspension

- PROTONIX oral suspension should be taken 30 minutes before a meal
- PROTONIX oral suspension should only be taken with applesauce or apple juice 30 minutes before a meal.
- PROTONIX should not be taken in or with water or other liquids, or with other foods. See "Directions for use" below.
- PROTONIX oral suspension should not be chewed or crushed.
- PROTONIX oral suspension packet should not be divided to make a smaller dose.

  Directions for use with applesauce:
  - Open packet.
  - Sprinkle granules on one teaspoonful of applesauce. Do not use any other foods. Do not crush or chew the granules.
  - Take within 10 minutes of putting the granules into the teaspoon of applesauce.
  - Take sips of water to make sure the granules are washed down into the stomach. Repeat water sips as necessary.

  Directions for use with apple juice:
  - Open packet.
  - Empty granules into a small cup or teaspoon with one teaspoonful of apple juice.
  - Stir the mix for 5 seconds (granules will not break up) and swallow it right away.
  - To make sure that the entire dose is taken, rinse the container once or twice with apple juice to get out any leftover granules. Swallow the apple juice right away.

Nasogastric Tube or Gastrostomy Tube Administration

For people who have a nasogastric (NG) tube or gastrostomy tube in place, PROTONIX oral suspension can be given as follows:

- Remove the plunger from the barrel of a 2 ounce (60 mL) catheter-tip syringe. Throw away the plunger.

- Connect the catheter tip of the syringe to a 16 French (or larger) tube.
- Hold the syringe attached to the tubing as high as possible while giving PROTONIX oral suspension to prevent any bending of the tubing.
- Empty the contents of the packet into the barrel of the syringe.
- Add 10 mL (2 teaspoonfuls) of apple juice and gently tap or shake the barrel of the syringe to help empty the syringe.
- Do this again at least two more times using the same amount of apple juice (10 mL or 2 teaspoonfuls) each time. No granules should be left in the syringe.

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United States Patent Number: 4,758,579, 7,544,370, 7,550,153 and 7,553,498 — Oral Suspension