PROTONIX (pantoprazole sodium) delayed-release tablets, for oral use

PROTONIX (pantoprazole sodium) for delayed-release oral suspension

Initial U.S. approval: 2000

—RECENT MAJOR CHANGES—

Warnings and Precautions, Fundic Gland Polyps (5.9) 06/2018
Warnings and Precautions, Interference with Investigations for Neuroendocrine Tumors (5.10) 12/2017

PROTONIX is a proton pump inhibitor (PPI) 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 (ZE) Syndrome (1.3)

—DOSED AND ADMINISTRATION—

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Term Treatment of Erosive Esophagitis</td>
<td>40 mg</td>
<td>Once Daily for up to 8 wks</td>
</tr>
<tr>
<td>Associated With GERD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children (5 years and older)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 15 kg to &lt; 40 kg</td>
<td>20 mg</td>
<td>Once Daily for up to 8 wks</td>
</tr>
<tr>
<td>≥ 40 kg</td>
<td>40 mg</td>
<td></td>
</tr>
<tr>
<td>Maintenance of Healing of Erosive Esophagitis</td>
<td>40 mg</td>
<td>Once Daily*</td>
</tr>
<tr>
<td>(2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological Hypersecretory Conditions</td>
<td>40 mg</td>
<td>Twice Daily</td>
</tr>
<tr>
<td>Including Zollinger-Ellison Syndrome (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Controlled studies did not extend beyond 12 months
See full prescribing information for administration instructions

—DOSE FORMS AND STRENGTHS—

• Delayed-Release Tablets: 20 mg and 40 mg pantoprazole (3)
• For Delayed-Release Oral Suspension: 40 mg pantoprazole (3)

—CONTRAINDICATIONS—

• Patients with known hypersensitivity to any component of the formulation or to substituted benzimidazoles (4)
• Patients receiving rilpivirine-containing products (4,7)

—WARNING AND PRECAUTIONS—

• Gastric Malignancy: In adults, symptomatic response does not preclude presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)
• Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.2)
• Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk of Clostridium difficile-associated diarrhea. (5.3)
• 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. (5.4)
• Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue PROTONIX and refer to specialist for evaluation. (5.5)
• Cyanocobalamin (Vitamin B-12) Deficiency: Daily long-term use (e.g., longer than 3 years) may lead to malabsorption or a deficiency of cyanocobalamin. (5.6)
• Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.7)
• Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.9)

—ADVERSE REACTIONS—

Most common adverse reactions are:

• For adult use (>2%): headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia. (6.1)
• For pediatric use (>4%): URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

—DRUG INTERACTIONS—

See full prescribing information for a list of clinically important drug interactions (7)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 06/2018
FULL PRESCRIBING INFORMATION: CONTENTS

1 INDICATIONS AND USAGE
1.1 Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)
1.2 Maintenance of Healing of Erosive Esophagitis
1.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison (ZE) Syndrome

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing Schedule
2.2 Administration Instructions

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS
5.1 Presence of Gastric Malignancy
5.2 Acute Interstitial Nephritis
5.3 Clostridium difficile-Associated Diarrhea
5.4 Bone Fracture
5.5 Cutaneous and Systemic Lupus Erythematosus
5.6 Cyanocobalamin (Vitamin B-12) Deficiency
5.7 Hypomagnesemia
5.8 Tumorigenicity
5.9 Fundic Gland Polyps
5.10 Interference with Investigations for Neuroendocrine Tumors
5.11 Interference with Urine Screen for THC
5.12 Concomitant Use of PROTONIX with Methotrexate

6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
6.2 Postmarketing Experience

7 DRUG INTERACTIONS

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES
14.1 Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)
14.2 Long-Term Maintenance of Healing of Erosive Esophagitis
14.3 Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* 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 (EE). 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 EE 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 (ZE) 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

<table>
<thead>
<tr>
<th>Indication</th>
<th>Dose</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-Term Treatment of Erosive Esophagitis Associated With GERD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>40 mg</td>
<td>Once daily for up to 8 weeks*</td>
</tr>
<tr>
<td>Children (5 years and older)</td>
<td></td>
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<tr>
<td>Adults</td>
<td>40 mg</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>40 mg</td>
<td>Twice daily**</td>
</tr>
</tbody>
</table>

* 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.

*** Controlled studies did not extend beyond 12 months

2.2 Administration Instructions

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

Table 2: Administration Instructions

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

* Do not split, chew, or crush PROTONIX Delayed-Release Tablets and PROTONIX For Delayed-Release Oral Suspension.

Take a missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular scheduled time. Do not take 2 doses at the same time.

PROTONIX Delayed-Release Tablets

Swallow PROTONIX Delayed-Release Tablets whole, with or without food in the stomach. For patients 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

Administer PROTONIX For Delayed-Release Oral Suspension 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 pantoprazole, yellow oval biconvex tablets imprinted with PROTONIX (brown ink) on one side
• 20 mg pantoprazole, yellow oval biconvex tablets imprinted with P20 (brown ink) on one side

For Delayed-Release Oral Suspension:

• 40 mg pantoprazole, 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 or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [see Adverse Reactions (6)].
• Proton pump inhibitors (PPIs), including PROTONIX, are contraindicated with rilpivirine-containing products [see Drug Interactions (7)].

5 WARNINGS AND PRECAUTIONS

5.1 Presence of Gastric Malignancy

In adults, symptomatic response to therapy with PROTONIX does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

5.2 Acute Interstitial Nephritis

Acute interstitial nephritis has been observed in patients taking PPIs including PROTONIX. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue PROTONIX if acute interstitial nephritis develops [see Contraindications (4)].

5.3 Clostridium difficile-Associated Diarrhea

Published observational studies suggest that PPI therapy like PROTONIX may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

5.4 Bone Fracture

Several published observational studies suggest that 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), Adverse Reactions (6.2)].

5.5 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematos cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving PROTONIX, discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

5.6 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.

5.7 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, and in most cases after a year of therapy. Serious adverse events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals
may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions (6.2)].

5.8 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)].

5.9 Fundic Gland Polyps

PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

5.10 Interference with Investigations for Neuroendocrine Tumors

Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop PROTONIX treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary [see Clinical Pharmacology (12.2)].

5.11 Interference with Urine Screen for THC

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs, including PROTONIX [see Drug Interactions (7)].

5.12 Concomitant Use of PROTONIX with Methotrexate

Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients [see Drug Interactions (7)].

6 ADVERSE REACTIONS

The following serious adverse reactions are described below and elsewhere in labeling:

- Acute Interstitial Nephritis [see Warnings and Precautions (5.2)]
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.3)]
- Bone Fracture [see Warnings and Precautions (5.4)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.5)]
• Cyanocobalamin (Vitamin B-12) Deficiency [see Warnings and Precautions (5.6)]
• Hypomagnesemia [see Warnings and Precautions (5.7)]
• Fundic Gland Polyps [see Warnings and Precautions (5.9)]

6.1 Clinical Trials Experience

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

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 H2-receptor antagonist, 46 patients on another PPI, 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%

<table>
<thead>
<tr>
<th>Reaction</th>
<th>PROTONIX (n=1473) %</th>
<th>Comparators (n=345) %</th>
<th>Placebo (n=82) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>12.2</td>
<td>12.8</td>
<td>8.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.8</td>
<td>9.6</td>
<td>4.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>7.0</td>
<td>5.2</td>
<td>9.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>6.2</td>
<td>4.1</td>
<td>6.1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.3</td>
<td>3.5</td>
<td>2.4</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3.9</td>
<td>2.9</td>
<td>3.7</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.0</td>
<td>2.9</td>
<td>1.2</td>
</tr>
<tr>
<td>Articulargia</td>
<td>2.8</td>
<td>1.4</td>
<td>1.2</td>
</tr>
</tbody>
</table>

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

Reference ID: 4274295
Musculoskeletal: myalgia

Nervous: depression, vertigo

Skin and Appendages: urticaria, rash, pruritus

Special Senses: blurred vision

Pediatric Patients

Safety of PROTONIX in the treatment of 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 (ZE) Syndrome

In clinical studies of ZE 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:

**Gastrointestinal Disorders:** fundic gland polyps

**General Disorders and Administration Conditions:** asthenia, fatigue, malaise

**Hematologic:** pancytopenia, agranulocytosis

**Hepatobiliary Disorders:** hepatocellular damage leading to jaundice and hepatic failure

**Immune System Disorders:** anaphylaxis (including anaphylactic shock), systemic lupus erythematosus

**Infections and Infestations:** *Clostridium difficile* associated diarrhea

**Investigations:** weight changes

**Metabolism and Nutritional Disorders:** hyponatremia, hypomagnesemia

**Musculoskeletal Disorders:** rhabdomyolysis, bone fracture

**Nervous:** ageusia, dysgeusia

**Psychiatric Disorders:** hallucination, confusion, insomnia, somnolence

**Renal and Urinary Disorders:** interstitial nephritis

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

7 DRUG INTERACTIONS

Table 4 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with PROTONIX and instructions for preventing or managing them.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.
### Table 4: Clinically Relevant Interactions Affecting Drugs Co-Administered with PROTONIX and Interactions with Diagnostics

#### Antiretrovirals

**Clinical Impact:** The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.

- Decreased exposure of some antiretroviral drugs (e.g., rilpivirine, atazanavir, and nelfinavir) when used concomitantly with pantoprazole may reduce antiviral effect and promote the development of drug resistance.
- Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase toxicity of the antiretroviral drugs.
- There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.

**Intervention:**

- Rilpivirine-containing products: Concomitant use with PROTONIX is contraindicated [see Contraindications (4)]. See prescribing information.

- Atazanavir: See prescribing information for atazanavir for dosing information.

- Nelfinavir: Avoid concomitant use with PROTONIX. See prescribing information for nelfinavir.

- Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities.

- Other antiretrovirals: See prescribing information.

#### Warfarin

**Clinical Impact:** Increased INR and prothrombin time in patients receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.

**Intervention:** Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.
### Clopidogrel

**Clinical Impact:** Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition [see Clinical Pharmacology (12.3)].

**Intervention:** No dose adjustment of clopidogrel is necessary when administered with an approved dose of PROTONIX.

### Methotrexate

**Clinical Impact:** Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted [see Warnings and Precautions (5.12)].

**Intervention:** A temporary withdrawal of PROTONIX may be considered in some patients receiving high-dose methotrexate.

### Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)

**Clinical Impact:** Pantoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

**Intervention:** Mycophenolate mofetil (MMF): Co-administration of pantoprazole sodium in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH [see Clinical Pharmacology (12.3)]. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PROTONIX and MMF. Use PROTONIX with caution in transplant patients receiving MMF.

See the prescribing information for other drugs dependent on gastric pH for absorption.
### Interactions with Investigations of Neuroendocrine Tumors

**Clinical Impact:** CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors [see Warnings and Precautions (5.10), Clinical Pharmacology (12.2)].

**Intervention:** Temporarily stop PROTONIX treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

### False Positive Urine Tests for THC

**Clinical Impact:** There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs [see Warnings and Precautions (5.11)].

**Intervention:** An alternative confirmatory method should be considered to verify positive results.

## 8 USE IN SPECIFIC POPULATIONS

### 8.1 Pregnancy

**Teratogenic Effects**

**Pregnancy Category C**

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

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day on a body surface area basis) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND) 4 through PND 21, the pups were administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in humans at a dose of 40 mg). There were no drug-related findings in maternal animals. During the preweaning dosing phase (PND 4 to 21) of the pups, there were increased mortality and/or moribundity and decreased body weight and body weight gain at 5 mg/kg/day (approximately equal exposures (AUC) in humans receiving the 40 mg dose) and higher doses. On PND 21, decreased mean femur length and weight and changes in
femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses. The femur findings included lower total area, bone mineral content and density, periosteal and endosteal circumference, and cross-sectional moment of inertia. There were no microscopic changes in the distal femur, proximal tibia, or stifle joints. Changes in bone parameters were partially reversible following a recovery period, with findings on PND 70 limited to lower femur metaphysis cortical/subcortical bone mineral density in female pups at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses.

There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk of fetal harm. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 of pantoprazole sodium. 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 sodium 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 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), 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.

**Animal Toxicity Data**

In a pre- and post-natal development study in rats, the pups were administered oral doses of pantoprazole at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in children aged 6 to 11 years at a dose of 40 mg) on postnatal day (PND 4) through PND 21, in addition to lactational exposure through milk. On PND 21, decreased mean femur length and weight and changes in femur bone mass and geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in children aged 6 to 11 years at the 40 mg dose) and higher doses. Changes in bone parameters were partially reversible following a recovery period.

In neonatal/juvenile animals (rats and dogs) toxicities were similar to those observed in adult animals, including gastric alterations, decreases in red cell mass, increases in lipids, enzyme induction and hepatocellular hypertrophy. An 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, was observed in the fundic mucosa of stomachs in repeated-dose studies. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

**8.5 Geriatric Use**

In short-term US clinical trials, EE 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.

**10 OVERDOSAGE**

Experience in patients taking very high doses of PROTONIX (greater than 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.

If overexposure to PROTONIX occurs, call your Poison Control Center at 1-800-222-1222 for current information on the management of poisoning or overdosage.

11 DESCRIPTION

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

![Structural formula of pantoprazole](image)

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 is supplied as a for delayed-release oral suspension in unit dose packets, available in one strength 40 mg pantoprazole, (equivalent to 45.1 mg of pantoprazole sodium), and as a delayed-release tablet, available in two strengths 20 mg pantoprazole (equivalent to 22.56 mg of pantoprazole sodium) and 40 mg pantoprazole (equivalent to 45.1 mg of pantoprazole sodium).

PROTONIX Delayed-Release Tablets contains 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 For Delayed-Release Oral Suspension contains 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 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 For Delayed-Release Oral Suspension, 40 mg has been shown to be comparable to PROTONIX 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 subjects. 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 5.
### Table 5: Effect of Single Daily Doses of Oral Pantoprazole on Intragastric pH

<table>
<thead>
<tr>
<th>Time</th>
<th>Placebo</th>
<th>20 mg</th>
<th>40 mg</th>
<th>80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 a.m. - 8 a.m.</td>
<td>1.3</td>
<td>2.9*</td>
<td>3.8*#</td>
<td>3.9*#</td>
</tr>
<tr>
<td>(24 hours)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8 a.m. - 10 p.m.</td>
<td>1.6</td>
<td>3.2*</td>
<td>4.4*#</td>
<td>4.8*#</td>
</tr>
<tr>
<td>(Daytime)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 p.m. - 8 a.m.</td>
<td>1.2</td>
<td>2.1*</td>
<td>3.0*</td>
<td>2.6*</td>
</tr>
<tr>
<td>(Nighttime)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 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 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 PPIs. 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)].

**Endocrine 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.

**12.3 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 6.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>Granules in Applesauce</th>
<th>Granules in Apple Juice</th>
<th>Granules in Nasogastric Tube</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (µg•hr/mL)</td>
<td>4.0 ± 1.5</td>
<td>4.0 ± 1.5</td>
<td>4.1 ± 1.7</td>
</tr>
<tr>
<td>C$_{max}$ (µg/mL)</td>
<td>2.0 ± 0.7</td>
<td>1.9 ± 0.5</td>
<td>2.2 ± 0.7</td>
</tr>
<tr>
<td>T$_{max}$ (hr)$^a$</td>
<td>2.0</td>
<td>2.5</td>
<td>2.0</td>
</tr>
</tbody>
</table>

$^a$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 $C_{\text{max}}$ 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 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Elimination

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.

Excretion

After a single oral or intravenous dose of $^{14}$C-labeled pantoprazole to healthy, normal metabolizer subjects, 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.
Specific Populations

Geriatric Patients

Only slight to moderate increases in the AUC (43%) and C_{\text{max}} (26%) of pantoprazole were found in elderly subjects (64 to 76 years of age) after repeated oral administration, compared with younger subjects [see Use in Specific Populations (8.5)].

Pediatric Patients

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 7).

<table>
<thead>
<tr>
<th></th>
<th>6-11 years (n=12)</th>
<th>12-16 years (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{\text{max}} (µg/mL)^a</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>t_{\text{max}} (h)^b</td>
<td>2.0</td>
<td>2.0</td>
</tr>
<tr>
<td>AUC (µg•h/mL)^a</td>
<td>6.9</td>
<td>5.5</td>
</tr>
<tr>
<td>CL/F (L/h)^b</td>
<td>6.6</td>
<td>6.8</td>
</tr>
</tbody>
</table>

^a Geometric mean values  
^b Median values

Male and Female Patients

There is a modest increase in pantoprazole AUC and C_{\text{max}} in women compared to men. However, weight-normalized clearance values are similar in women and men.
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.

*Patients with Renal Impairment*

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects.

*Patients with 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. Doses higher than 40 mg/day have not been studied in hepatically impaired patients.

*Drug Interaction Studies*

*Effect of Other Drugs on Pantoprazole*

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] and clopidogrel), 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.

*Effect of Pantoprazole on Other Drugs*

**Clopidogrel**

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. In a crossover clinical study, 66 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with pantoprazole (80 mg at the same time as clopidogrel) for 5 days. On Day 5, the mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (geometric mean ratio was 86%, with 90% CI of 79 to 93%) when pantoprazole was coadministered with clopidogrel as compared to clopidogrel administered alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 µM ADP) was correlated with the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.
Mycophenolate Mofetil (MMF)

Administration of pantoprazole 40 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of pantoprazole to 12 healthy subjects in a cross-over study resulted in a 57% reduction in the Cmax and 27% reduction in the AUC of MPA. Transplant patients receiving approximately 2000 mg per day of MMF (n=12) were compared to transplant patients receiving approximately the same dose of MMF and pantoprazole 40 mg per day (n=21). There was a 78% reduction in the Cmax and a 45% reduction in the AUC of MPA in patients receiving both pantoprazole and MMF [see Drug Interactions (7)].

Other Drugs

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, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, diclofenac, naproxen, piroxicam, and oral contraceptives [levonorgestrel/ethinyl estradiol]). In other in vivo studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole.

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 heptically impaired.

Antacids

There was also no interaction with concomitantly administered antacids.

12.5 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 hours in adults, they still have minimal accumulation (23% or less) 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 pantoprazole 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 with 40 mg/day. In the gastric fundus, treatment with 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 with 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 with 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus with 200 mg/kg/day. In the liver, treatment with 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment with 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 of pantoprazole, approximately 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment with 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 of pantoprazole, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment with 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment with 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).
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 8.

<table>
<thead>
<tr>
<th>Week (n = 153)</th>
<th>PROTONIX 10 mg daily</th>
<th>PROTONIX 20 mg daily</th>
<th>PROTONIX 40 mg daily</th>
<th>Placebo (n = 68)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>45.6%⁺</td>
<td>58.4%⁻⁺ #</td>
<td>75.0%⁻⁺ *</td>
<td>14.3%</td>
</tr>
<tr>
<td>8</td>
<td>66.0%⁺</td>
<td>83.5%⁺ #</td>
<td>92.6%⁺ *</td>
<td>39.7%</td>
</tr>
</tbody>
</table>

⁺ (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 9.

<table>
<thead>
<tr>
<th>Week (n = 72)</th>
<th>PROTONIX 20 mg daily</th>
<th>PROTONIX 40 mg daily</th>
<th>Nizatidine 150 mg twice daily (n = 70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>61.4%⁺</td>
<td>64.0%⁺</td>
<td>22.2%</td>
</tr>
<tr>
<td>8</td>
<td>79.2%⁺</td>
<td>82.9%⁺</td>
<td>41.4%</td>
</tr>
</tbody>
</table>

⁺ (p < 0.001) PROTONIX versus nizatidine

Reference ID: 4274295
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 EE 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 10, 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 10: Long-Term Maintenance of Healing of Erosive Gastroesophageal Reflux Disease (GERD Maintenance): Percentage of Patients Who Remained Healed**

<table>
<thead>
<tr>
<th></th>
<th>PROTONIX 20 mg daily</th>
<th>PROTONIX 40 mg daily</th>
<th>Ranitidine 150 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study 1</strong></td>
<td>n = 75</td>
<td>n = 74</td>
<td>n = 75</td>
</tr>
<tr>
<td>Month 1</td>
<td>91*</td>
<td>99*</td>
<td>68</td>
</tr>
<tr>
<td>Month 3</td>
<td>82*</td>
<td>93*#</td>
<td>54</td>
</tr>
<tr>
<td>Month 6</td>
<td>76*</td>
<td>90*#</td>
<td>44</td>
</tr>
<tr>
<td>Month 12</td>
<td>70*</td>
<td>86*#</td>
<td>35</td>
</tr>
</tbody>
</table>

Reference ID: 4274295
Table 10: Long-Term Maintenance of Healing of Erosive Gastroesophageal Reflux Disease (GERD Maintenance): Percentage of Patients Who Remain Healed

<table>
<thead>
<tr>
<th></th>
<th>PROTONIX 20 mg daily</th>
<th>PROTONIX 40 mg daily</th>
<th>Ranitidine 150 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 2</td>
<td>n = 74</td>
<td>n = 88</td>
<td>n = 84</td>
</tr>
<tr>
<td>Month 1</td>
<td>89*</td>
<td>92**</td>
<td>62</td>
</tr>
<tr>
<td>Month 3</td>
<td>78*</td>
<td>91**</td>
<td>47</td>
</tr>
<tr>
<td>Month 6</td>
<td>72*</td>
<td>88**</td>
<td>39</td>
</tr>
<tr>
<td>Month 12</td>
<td>72*</td>
<td>83*</td>
<td>37</td>
</tr>
</tbody>
</table>

* (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 11.

Table 11: Number of Episodes of Heartburn (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>PROTONIX 40 mg daily</th>
<th>Ranitidine 150 mg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>5.1 ± 1.6*</td>
<td>18.3 ± 1.6</td>
</tr>
<tr>
<td>Nighttime</td>
<td>3.9 ± 1.1*</td>
<td>11.9 ± 1.1</td>
</tr>
<tr>
<td>Month 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime</td>
<td>2.9 ± 1.5*</td>
<td>17.5 ± 1.5</td>
</tr>
<tr>
<td>Nighttime</td>
<td>2.5 ± 1.2*</td>
<td>13.8 ± 1.3</td>
</tr>
</tbody>
</table>

* (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 yellow, oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side containing 40 mg pantoprazole and are available as follows:

- NDC 0008-0841-81, bottles of 90

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

- NDC 0008-0843-81, bottles of 90

PROTONIX (pantoprazole sodium) For Delayed-Release Oral Suspension is supplied as pale yellowish to dark brownish, enteric-coated granules containing 40 mg pantoprazole in a 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

Advise the patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Gastric Malignancy
Advise patients to return to their healthcare provider if they have a suboptimal response or an early symptomatic relapse [see Warnings and Precautions (5.1)].

Acute Interstitial Nephritis
Advise patients to call their healthcare provider immediately if they experience signs and/or symptoms associated with acute interstitial nephritis [see Warnings and Precautions (5.2)].

Clostridium difficile-Associated Diarrhea
Advise patients to immediately call their healthcare provider if they experience diarrhea that does not improve [see Warnings and Precautions (5.3)].

Bone Fracture
Advise patients to report any fractures, especially of the hip, wrist or spine, to their healthcare provider [see Warnings and Precautions (5.4)].
Cutaneous and Systemic Lupus Erythematosus
Advise patients to immediately call their healthcare provider for any new or worsening of symptoms associated with cutaneous or systemic lupus erythematosus [see Warnings and Precautions (5.5)].

Cyanocobalamin (Vitamin B-12) Deficiency
Advise patients to report any clinical symptoms that may be associated with cyanocobalamin deficiency to their healthcare provider if they have been receiving PROTONIX for longer than 3 years [see Warnings and Precautions (5.6)].

Hypomagnesemia
Advise patients to report any clinical symptoms that may be associated with hypomagnesemia to their healthcare provider, if they have been receiving PROTONIX for at least 3 months [see Warnings and Precautions (5.7)].

Drug Interactions
Instruct patients to inform their healthcare provider of any other medications they are currently taking, including rilpivirine-containing products [see Contraindications (4)] digoxin [see Warnings and Precautions (5.7)] and high dose methotrexate [see Warnings and Precautions (5.12)].

Pregnancy
Inform female patients of reproductive potential that PROTONIX may cause fetal harm and to inform their prescriber of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

Administration
- Do not split, crush, or chew PROTONIX For Delayed-Release Oral Suspension and PROTONIX Delayed-Release Tablets.
- PROTONIX oral suspension packet is a fixed dose and cannot be divided to make a smaller dose.
- Swallow PROTONIX Delayed-Release Tablets whole, with or without food in the stomach.
- Concomitant administration of antacids does not affect the absorption of PROTONIX Delayed-Release Tablets.
- Take PROTONIX For Delayed-Release Oral Suspension approximately 30 minutes before a meal.
- Administer PROTONIX For Delayed-Release Oral Suspension in apple juice or applesauce, as described in the Instructions for Use. Do not administer in water, other liquids, or foods.
- For patients with a nasogastric (NG) or gastrostomy tube, PROTONIX For Delayed-Release Oral Suspension can be administered with apple juice, as described in the Instructions for Use.
- Take a missed dose as soon as possible. If it is almost time for the next dose, skip the missed dose and take the next dose at the regular scheduled time. Do not take 2 doses at the same time.
This product’s label may have been updated. For current full prescribing information, please visit www.pfizer.com.

under license from
Takeda GmbH
D78467 Konstanz, Germany

LAB-0459-16.0
### MEDICATION GUIDE
**PROTONIX (pro-TAH-nix)**
(pantoprazole sodium)
delayed-release tablets
and
**PROTONIX (pro-TAH-nix)**
(pantoprazole sodium)
for delayed-release oral suspension

**What is the most important information I should know about PROTONIX?**

You should take PROTONIX exactly as prescribed, at the lowest dose possible and for the shortest time needed.

PROTONIX may help your acid-related symptoms, but you could still have serious stomach problems. Talk with your doctor.

PROTONIX can cause serious side effects, including:

- **A type of kidney problem (acute interstitial nephritis).** Some people who take proton pump inhibitor (PPI) medicines, including PROTONIX, may develop a kidney problem called acute interstitial nephritis that can happen at any time during treatment with PROTONIX. Call your doctor right away if you have a decrease in the amount that you urinate or if you have blood in your urine.

- **Diarrhea caused by an infection (Clostridium difficile) in your intestines.** Call your doctor right away if you have watery stools or stomach pain that does not go away. You may or may not have a fever.

- **Bone fractures (hip, wrist, or spine).** Bone fractures in the hip, wrist, or spine may happen in people who take multiple daily doses of PPI medicines and for a long period of time (a year or longer). Tell your doctor if you have a bone fracture, especially in the hip, wrist, or spine.

- **Certain types of lupus erythematosus.** Lupus erythematosus is an autoimmune disorder (the body’s immune cells attack other cells or organs in the body). Some people who take PPI medicines, including PROTONIX, may develop certain types of lupus erythematosus or have worsening of the lupus they already have. Call your doctor right away if you have new or worsening joint pain or a rash on your cheeks or arms that gets worse in the sun.

Talk to your doctor about your risk of these serious side effects.

PROTONIX can have other serious side effects. See “What are the possible side effects of PROTONIX?”

### What is PROTONIX?

A prescription medicine called a proton pump inhibitor (PPI) used to reduce the amount of acid in your stomach.

**In adults,** PROTONIX is used for:

- up to 8 weeks for the healing and symptom relief of acid-related damage to the lining of the esophagus (called erosive esophagitis or EE). Your doctor may prescribe another 8 weeks of PROTONIX in patients whose EE does not heal.

- maintaining healing of EE and to help prevent the return of heartburn symptoms caused by GERD. It is not known if PROTONIX is safe and effective when used for longer than 12 months for this purpose.

- the long-term treatment of conditions where your stomach makes too much acid. This includes a rare condition called Zollinger-Ellison Syndrome.

**In children 5 years of age and older,** PROTONIX is used for:

- up to 8 weeks for the healing and symptom relief of EE.

  It is not known if PROTONIX is safe if used longer than 8 weeks in children.

  PROTONIX is not for use in children under 5 years of age.

  It is not known if PROTONIX is safe and effective in children for treatment other than EE.
Do not take PROTONIX if you are:
- allergic to pantoprazole sodium, any other PPI medicine, or any of the ingredients in PROTONIX. See the end of this Medication Guide for a complete list of ingredients.
- taking a medicine that contains rilpivirine (EDURANT, COMPLERA, ODEFSEY) used to treat HIV-1 (Human Immunodeficiency Virus).

Before taking PROTONIX, tell your doctor about all of your medical conditions, including if you:
- have low magnesium levels in your blood.
- are pregnant or plan to become pregnant. PROTONIX may harm your unborn baby. Tell your doctor if you become pregnant or think you may be pregnant during treatment with PROTONIX.
- are breastfeeding or plan to breastfeed. PROTONIX can pass into your breast milk. You and your doctor should decide if you will take PROTONIX or breastfeed. You should not do both. Talk with your doctor about the best way to feed your baby if you take PROTONIX.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. Especially tell your doctor if you take methotrexate (Otrexup, Rasuvo, Trexall, XATMEP), digoxin (LANOXIN), or a water pill (diuretic).

How should I take PROTONIX?
- Take PROTONIX exactly as prescribed by your doctor.
  PROTONIX delayed-release tablets (PROTONIX tablets):
  o Do not split, chew, or crush PROTONIX tablets.
  o Swallow PROTONIX tablets whole, with or without food.
  o Tell your doctor if you are not able to swallow your PROTONIX tablet.
  o You may use antacids while taking PROTONIX tablets.
  PROTONIX for delayed-release oral suspension (PROTONIX for oral suspension):
  o Do not split, chew, or crush PROTONIX for oral suspension.
  o Take PROTONIX for oral suspension about 30 minutes before a meal.
  o PROTONIX for oral suspension should only be given by mouth mixed in apple juice or applesauce or through a nasogastric (NG) tube or gastrostomy tube mixed in apple juice. Do not mix PROTONIX for oral suspension in liquids other than apple juice or foods other than applesauce.
  o Do not divide a packet of PROTONIX for oral suspension to make a smaller dose.
  o See the “Instructions for Use” at the end of this Medication Guide for instructions on how to mix and give the suspension through an NG tube or gastrostomy tube mixed in apple juice.
- If you miss a dose of PROTONIX, take it as soon as possible. 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 2 doses at the same time.
- If you take too much PROTONIX, call your doctor or your poison control center at 1-800-222-1222 right away or go to the nearest emergency room.

What are the possible side effects of PROTONIX?
PROTONIX can cause serious side effects, including:
- See “What is the most important information I should know about PROTONIX?”
- **Low vitamin B-12 levels** in your body can happen in people who have taken PROTONIX for a long time (more than 3 years). Tell your doctor if you have symptoms of low vitamin B-12 levels, including shortness of breath, lightheadedness, irregular heartbeat, muscle weakness, pale skin, feeling tired, mood changes, and tingling or numbness in the arms and legs.
- **Low magnesium levels in your body** can happen in people who have taken PROTONIX for at least 3 months. Tell your doctor if you have symptoms of low magnesium levels, including seizures, dizziness, irregular heartbeat, jitteriness, muscle aches or weakness, and spasms of hands, feet or voice.
- **Stomach growths (fundic gland polyps).** People who take PPI medicines for a long time have an increased risk of developing a certain type of stomach growths called fundic gland polyps, especially after taking PPI medicines for more than 1 year.

The most common side effects of PROTONIX in adults include: headache, diarrhea, nausea, stomach-area (abdominal) pain, vomiting, gas, dizziness, and joint pain.
The most common side effects of PROTONIX in children include: upper respiratory infection,
headache, fever, diarrhea, vomiting, rash, and stomach-area (abdominal) pain. These are not all the possible side effects of PROTONIX. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

<table>
<thead>
<tr>
<th>How should I store PROTONIX?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Store PROTONIX at room temperature between 68°F to 77°F (20°C to 25°C).</td>
</tr>
<tr>
<td>Keep PROTONIX and all medicines out of the reach of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General information about the safe and effective use of PROTONIX.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. 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 that you have. It may harm them. You can ask your doctor or pharmacist for information about PROTONIX that is written for health professionals.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>What are the ingredients in PROTONIX?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active ingredient:</strong> pantoprazole sodium sesquihydrate</td>
</tr>
<tr>
<td><strong>Inactive ingredients in PROTONIX delayed-release tablets:</strong> 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.</td>
</tr>
<tr>
<td><strong>Inactive ingredients in PROTONIX for delayed-release oral suspension:</strong> crospovidone, hypromellose, methacrylic acid copolymer, microcrystalline cellulose, polysorbate 80, povidone, sodium carbonate, sodium lauryl sulfate, talc, titanium dioxide, triethyl citrate, and yellow ferric oxide.</td>
</tr>
</tbody>
</table>

For more information go to www.pfizer.com or call 1-800-438-1985.
Instructions for Use
PROTONIX (pro-TAH-nix)
pantoprazole sodium
for delayed-release oral suspension

PROTONIX for delayed-release oral suspension (PROTONIX for oral suspension):

Important information:

• Do not split, chew, or crush PROTONIX for oral suspension.
• Take PROTONIX for oral suspension about 30 minutes before a meal.
• PROTONIX for oral suspension:
  o should only be taken with applesauce or apple juice.
  o should not be mixed in water or other liquids, or other foods.
  o packet should not be divided to make a smaller dose.

Taking PROTONIX for oral suspension with applesauce:

1. Open the packet of PROTONIX for oral suspension.
2. Sprinkle all of the granules in the packet on 1 teaspoon of applesauce.
3. Swallow the granules and applesauce within 10 minutes of putting the granules on the teaspoon of applesauce.
4. Take sips of water to make sure the granules are washed down into the stomach. Take more sips of water as needed.

Taking PROTONIX for oral suspension with apple juice:

1. Open the packet of PROTONIX for oral suspension.
2. Empty all of the granules in the packet into a small cup that contains 1 teaspoon of apple juice.
3. Stir the granules-apple juice mixture for 5 seconds. The granules will not break up.
4. Swallow the mixture right away.
5. To make sure that the entire dose is taken, add more apple juice to the cup, stir and swallow the apple juice right away.
6. Repeat step 5 if there are granules left in the cup.

Giving PROTONIX for oral suspension through a nasogastric (NG) tube or gastrostomy tube:

• PROTONIX for oral suspension may be given through an NG tube or gastrostomy tube that is size 16 French or larger. Do not give PROTONIX for oral suspension through an NG tube or gastrostomy tube smaller than size 16 French.
• Mix PROTONIX for oral suspension only in apple juice when giving through an NG tube or gastrostomy tube.
  1. Remove the plunger from a 60 mL (2 ounce) catheter-tip syringe. Throw away the plunger.
  2. Connect the tip of the catheter-tip syringe to the NG tube or gastrostomy tube.
  3. Hold the syringe attached to the NG tube or gastrostomy tube as high as possible while giving PROTONIX for oral suspension to prevent the tubing from bending.
  4. Open the packet of PROTONIX for oral suspension.
  5. Empty all the granules in the packet into the catheter-tip syringe.
  6. Add 10 mL (2 teaspoons) of apple juice into the catheter-tip syringe and gently tap or shake the syringe to help empty the syringe.
7. Repeat step 6 at least 2 more times until there are no granules left in the catheter-tip syringe.

**How should I store PROTONIX?**

Store PROTONIX at room temperature between 68°F to 77°F (20°C to 25°C).

**Keep PROTONIX and all medicines out of the reach of children.**

This Medication Guide and Instructions for Use has been approved by the U.S. Food and Drug Administration.

This product’s label may have been updated. For current full prescribing information, please go to www.pfizer.com.

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Takeda GmbH
D78467 Konstanz, Germany

LAB-0574-12.0

Revised: June 2018
CONTRAINDICATIONS

1. Patients receiving rilpivirine-containing products. (4,7)

WARNINGS AND PRECAUTIONS

1. Gastric Malignancy: In adults, symptomatic response to therapy with PROTONIX I.V. does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing. (5.1)

2. Hypersensitivity and Severe Skin Reactions: Anaphylaxis has been reported. (5.2)

3. Injection Site Reactions: Thrombophlebitis is associated with the administration of intravenous pantoprazole. (5.3)

4. Potential Exacerbation of Zinc Deficiency: Consider zinc supplementation in patients who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously. (5.4)

5. Acute Interstitial Nephritis: Observed in patients taking PPIs. (5.5)

6. Clostridium difficile-Associated Diarrhea: PPI therapy may be associated with increased risk. (5.6)

7. 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. (5.7)

8. Cutaneous and Systemic Lupus Erythematosus: Mostly cutaneous; new onset or exacerbation of existing disease; discontinue PROTONIX I.V. and refer to specialist for evaluation. (5.8)

9. Hepatic Effects: Elevations of transaminases observed. (5.9)

10. Hypomagnesemia: Reported rarely with prolonged treatment with PPIs. (5.10)

11. Fundic Gland Polyps: Risk increases with long-term use, especially beyond one year. Use the shortest duration of therapy. (5.11)

ADVERSE REACTIONS

Most common adverse reactions (>2%) are: headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Pfizer Inc. at 1-800-438-1985 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

See the full prescribing information for a list of clinically important drug interactions (7)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 06/2018

PROTONIX I.V. (pantoprazole sodium) for injection, for intravenous use

Initial U.S. approval: 2000

References

1. INDICATIONS AND USAGE

2. DOSAGE AND ADMINISTRATION

3. CONTRAINDICATIONS

4. WARNINGS AND PRECAUTIONS

5. ADVERSE REACTIONS

6. DRUG INTERACTIONS

7. USE IN SPECIFIC POPULATIONS

8. CLINICAL PHARMACOLOGY

9. NONCLINICAL TOXICOLOGY

10. CLINICAL STUDIES

11. HOW SUPPLIED/STORAGE AND HANDLING

12. PATIENT COUNSELING INFORMATION

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

1  INDICATIONS AND USAGE

1.1 Gastroesophageal Reflux Disease Associated with a History of Erosive Esophagitis
PROTONIX I.V. is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE).

Safety and efficacy of PROTONIX I.V. as a treatment of patients with GERD and a history of EE for more than 10 days have not been demonstrated.

1.2 Pathological Hypersecretion Including Zollinger-Ellison Syndrome
PROTONIX I.V. is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison (ZE) Syndrome in adults.

2  DOSAGE AND ADMINISTRATION

2.1 Dosage for Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis
The recommended adult dosage of PROTONIX I.V. is 40 mg given once daily by intravenous infusion for 7 to 10 days.

Discontinue treatment with PROTONIX® I.V. as soon as the patient is able to receive treatment with PROTONIX Delayed-Release Tablets or Oral Suspension.

Data on the safe and effective dosing for conditions other than those described [see Indications and Usage (1)] such as life-threatening upper gastrointestinal bleeds, are not available.

PROTONIX I.V. 40 mg once daily does not raise gastric pH to levels sufficient to contribute to the treatment of such life-threatening conditions.

2.2 Preparation and Administration Instructions for Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

Only for intravenous infusion; other parenteral routes of administration are not recommended.

Fifteen Minute Infusion

1. Reconstitute PROTONIX I.V. with 10 mL of 0.9% Sodium Chloride Injection, USP.

2. Further dilute with 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a final concentration of approximately 0.4 mg/mL.

3. Inspect the diluted PROTONIX I.V. solution visually for particular matter and discoloration prior to and during administration.

4. Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.
Storage

The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light.

Do not freeze the reconstituted solution.

Two Minute Infusion

1. Reconstitute PROTONIX I.V. with 10 mL of 0.9% Sodium Chloride Injection, USP, to a final concentration of approximately 4 mg/mL.

2. Inspect the diluted PROTONIX I.V. solution visually for particular matter and discoloration prior to and during administration.

3. Administer intravenously over a period of at least 2 minutes.

Storage

The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion and does not need to be protected from light.

Do not freeze the reconstituted solution.

2.3 Dosage for Pathological Hypersecretion Including Zollinger-Ellison Syndrome

The recommended adult dosage of PROTONIX I.V. is 80 mg intravenously every 12 hours. The frequency of dosing can be adjusted to individual patient needs based on acid output measurements. In those patients who need a higher dosage, 80 mg intravenously every 8 hours is expected to maintain acid output below 10 mEq/h. Daily doses higher than 240 mg or administered for more than 6 days have not been studied [see Clinical Studies (14)]. Transition from oral to intravenous and from intravenous to oral formulations of gastric acid inhibitors should be performed in such a manner to ensure continuity of effect of suppression of acid secretion. Patients with ZE Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

2.4 Preparation and Administration Instructions for Pathological Hypersecretion Including Zollinger-Ellison Syndrome

Only for intravenous infusion; other parenteral routes of administration are not recommended.

Fifteen Minute Infusion

1. Reconstitute each vial of PROTONIX I.V. with 10 mL of 0.9% Sodium Chloride Injection, USP.

2. Combine the contents of the two vials and further dilute with 80 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL.
3. Inspect the diluted PROTONIX I.V. solution visually for particular matter and discoloration prior to and during administration.

4. Administer intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Storage
The reconstituted solution may be stored for up to 6 hours at room temperature prior to further dilution. The admixed solution may be stored at room temperature and must be used within 24 hours from the time of initial reconstitution. Both the reconstituted solution and the admixed solution do not need to be protected from light.

Do not freeze the reconstituted solution.

Two Minute Infusion
1. Reconstitute PROTONIX I.V. with 10 mL of 0.9% Sodium Chloride Injection, USP, per vial to a final concentration of approximately 4 mg/mL.

2. Inspect the diluted PROTONIX I.V. solution visually for particular matter and discoloration prior to and during administration.

3. Administer the total volume from both vials intravenously over a period of at least 2 minutes.

Storage
The reconstituted solution may be stored for up to 24 hours at room temperature prior to intravenous infusion and does not need to be protected from light.

Do not freeze the reconstituted solution.

2.5 Compatibility Information

- Administer PROTONIX I.V. intravenously through a dedicated line or through a Y-site.
- Flush the intravenous line before and after administration of PROTONIX I.V. with either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer’s Injection, USP.
- When administered through a Y-site, PROTONIX I.V. is compatible with the following solutions: 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer’s Injection, USP.
- Midazolam HCl has been shown to be incompatible with Y-site administration of PROTONIX I.V.
- PROTONIX I.V. may not be compatible with products containing zinc [see Warnings and Precautions (5.4)].
- When PROTONIX I.V. is administered through a Y-site, immediately stop use if precipitation or discoloration occurs.
3 DOSAGE FORMS AND STRENGTHS
For Injection: 40 mg of pantoprazole white to off-white freeze-dried powder in a single-dose vial for reconstitution.

4 CONTRAINDICATIONS
- PROTONIX I.V. is contraindicated in patients with known hypersensitivity reactions including anaphylaxis to the formulation [see Warnings and Precautions (5.2)] or any substituted benzimidazole. Hypersensitivity reactions may include anaphylaxis, anaphylactic shock, angioedema, bronchospasm, acute interstitial nephritis, and urticaria [see Adverse Reactions (6)].
- Proton pump inhibitors (PPIs), including PROTONIX I.V., are contraindicated in patients receiving rilpivirine-containing products [see Drug Interactions (7)].

5 WARNINGS AND PRECAUTIONS
5.1 Presence of Gastric Malignancy
In adults, symptomatic response to therapy with PROTONIX I.V. does not preclude the presence of gastric malignancy. Consider additional follow-up and diagnostic testing in adult patients who have a suboptimal response or an early symptomatic relapse after completing treatment with a PPI. In older patients, also consider an endoscopy.

5.2 Hypersensitivity and Severe Skin Reactions
Anaphylaxis and other serious reactions such as erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN) have been reported with use of PROTONIX I.V. These may require emergency medical treatment [see Adverse Reactions (6.2)].

5.3 Injection Site Reactions
Thrombophlebitis was associated with the administration of PROTONIX I.V.

5.4 Potential for Exacerbation of Zinc Deficiency
PROTONIX I.V. contains edetate disodium (the salt form of EDTA), a chelator of metal ions including zinc. Therefore, zinc supplementation should be considered in patients treated with PROTONIX I.V. who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously [see Dosage and Administration (2.5)].

5.5 Acute Interstitial Nephritis
Acute interstitial nephritis has been observed in patients taking PPIs including PROTONIX I.V. Acute interstitial nephritis may occur at any point during PPI therapy and is generally attributed to an idiopathic hypersensitivity reaction. Discontinue PROTONIX I.V. if acute interstitial nephritis develops [see Contraindications (4)].

5.6 Clostridium difficile-Associated Diarrhea
Published observational studies suggest that PPI therapy like PROTONIX I.V. may be associated with an increased risk of Clostridium difficile associated diarrhea, especially in hospitalized
patients. This diagnosis should be considered for diarrhea that does not improve [see Adverse Reactions (6.2)].

Patients should use the lowest dose and shortest duration of PPI therapy appropriate to the condition being treated.

5.7 Bone Fracture

Several published observational studies suggest that 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 (2.2, 2.4), Adverse Reactions (6)].

5.8 Cutaneous and Systemic Lupus Erythematosus

Cutaneous lupus erythematosus (CLE) and systemic lupus erythematosus (SLE) have been reported in patients taking PPIs, including pantoprazole sodium. These events have occurred as both new onset and an exacerbation of existing autoimmune disease. The majority of PPI-induced lupus erythematos cases were CLE.

The most common form of CLE reported in patients treated with PPIs was subacute CLE (SCLE) and occurred within weeks to years after continuous drug therapy in patients ranging from infants to the elderly. Generally, histological findings were observed without organ involvement.

Systemic lupus erythematosus (SLE) is less commonly reported than CLE in patients receiving PPIs. PPI associated SLE is usually milder than non-drug induced SLE. Onset of SLE typically occurred within days to years after initiating treatment primarily in patients ranging from young adults to the elderly. The majority of patients presented with rash; however, arthralgia and cytopenia were also reported.

Avoid administration of PPIs for longer than medically indicated. If signs or symptoms consistent with CLE or SLE are noted in patients receiving PROTONIX I.V., discontinue the drug and refer the patient to the appropriate specialist for evaluation. Most patients improve with discontinuation of the PPI alone in 4 to 12 weeks. Serological testing (e.g. ANA) may be positive and elevated serological test results may take longer to resolve than clinical manifestations.

5.9 Hepatic Effects

Mild, transient transaminase elevations have been observed in clinical studies. The clinical significance of this finding in a large population of subjects administered PROTONIX I.V. is unknown [see Adverse Reactions (6)].

5.10 Hypomagnesemia

Hypomagnesemia, symptomatic and asymptomatic, has been reported rarely in patients treated with PPIs for at least three months, and in most cases after a year of therapy. Serious adverse
events include tetany, arrhythmias, and seizures. In most patients, treatment of hypomagnesemia required magnesium replacement and discontinuation of the PPI.

For patients expected to be on prolonged treatment or who take PPIs with medications such as digoxin or drugs that may cause hypomagnesemia (e.g., diuretics), health care professionals may consider monitoring magnesium levels prior to initiation of PPI treatment and periodically [see Adverse Reactions (6.2)].

5.11 Fundic Gland Polyps
PPI use is associated with an increased risk of fundic gland polyps that increases with long-term use, especially beyond one year. Most PPI users who developed fundic gland polyps were asymptomatic and fundic gland polyps were identified incidentally on endoscopy. Use the shortest duration of PPI therapy appropriate to the condition being treated.

5.12 Interference with Investigations for Neuroendocrine Tumors
Serum chromogranin A (CgA) levels increase secondary to drug-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors. Healthcare providers should temporarily stop PROTONIX I.V. treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary [see Clinical Pharmacology (12.2)].

5.13 Interference with Urine Screen for THC
Pantoprazole sodium may produce false-positive urine screen for THC (tetrahydrocannabinol) [see Drug Interactions (7)].

5.14 Concomitant Use of PROTONIX I.V. with Methotrexate
Literature suggests that concomitant use of PPIs with methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicities. In high-dose methotrexate administration, a temporary withdrawal of the PPI may be considered in some patients [see Drug Interactions (7)].

6 ADVERSE REACTIONS
The following serious adverse reactions are described below and elsewhere in labeling:

- Hypersensitivity and Severe Skin Reactions [see Warnings and Precautions (5.2)]
- Injection Site Reactions [see Warnings and Precautions (5.3)]
- Potential for Exacerbation of Zinc Deficiency [see Warnings and Precautions (5.4)]
- Acute Interstitial Nephritis [see Warnings and Precautions (5.5)]
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.6)]
- Bone Fracture [see Warnings and Precautions (5.7)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.8)]
6.1 Clinical Trials 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.

Worldwide, approximately 80,500 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment.

Gastroesophageal Reflux Disease (GERD)

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 H₂-receptor antagonist, 46 patients on another PPI, and 82 patients on placebo. The most frequently occurring adverse reactions are listed in Table 1.

The number of patients treated in comparative studies with PROTONIX I.V. is limited; however, the adverse reactions seen were similar to those seen in the oral studies. Thrombophlebitis was the only new adverse reaction identified with PROTONIX I.V.

Table 1: Adverse Reactions Reported in Clinical Trials of Adult Patients with GERD at a Frequency of > 2%

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

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

Body as a Whole: allergic reaction, fever, photosensitivity reaction, facial edema, thrombophlebitis (I.V. only)

Gastrointestinal: constipation, dry mouth, hepatitis

Hematologic: leukopenia (reported in ex-US clinical trials only), thrombocytopenia
**Metabolic/Nutritional:** elevated CPK (creatine phosphokinase), generalized edema, elevated triglycerides, liver function tests abnormal

**Musculoskeletal:** myalgia

**Nervous:** depression, vertigo

**Skin and Appendages:** urticaria, rash, pruritus

**Special Senses:** blurred vision

**Zollinger-Ellison (ZE) Syndrome**

In clinical studies of ZE Syndrome, adverse reactions reported in 35 patients administered PROTONIX I.V. doses of 80 mg to 240 mg per 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 and PROTONIX I.V. 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:

**General Disorders and Administration Conditions:** asthenia, fatigue, malaise

**Immune System Disorders:** anaphylaxis (including anaphylactic shock), systemic lupus erythematosus

**Investigations:** weight changes

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

**Musculoskeletal Disorders:** rhabdomyolysis, bone fracture

**Renal and Urinary Disorders:** interstitial nephritis

**Hepatobiliary Disorders:** hepatocellular damage leading to jaundice and hepatic failure

**Psychiatric Disorder:** hallucinations, confusion, insomnia, somnolence

**Metabolism and Nutritional Disorders:** hyponatremia, hypomagnesemia

**Infections and Infestations:** Clostridium difficile associated diarrhea

**Hematologic:** pancytopenia, agranulocytosis

**Nervous:** ageusia, dysgeusia

**Gastrointestinal Disorders:** fundic gland polyps

### 7 Drug Interactions

Table 2 includes drugs with clinically important drug interactions and interaction with diagnostics when administered concomitantly with PROTONIX I.V. and instructions for preventing or managing them.

Consult the labeling of concomitantly used drugs to obtain further information about interactions with PPIs.
## Table 2: Clinically Relevant Interactions Affecting Drugs Co-Administered with PROTONIX I.V. and Interaction with Diagnostics

<table>
<thead>
<tr>
<th>Antiretrovirals</th>
<th>Clinical Impact: The effect of PPIs on antiretroviral drugs is variable. The clinical importance and the mechanisms behind these interactions are not always known.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Decreased exposure of some antiretroviral drugs (e.g., rilpivirine atazanavir, and nelfinavir) when used concomitantly with pantoprazole may reduce antiviral effect and promote the development of drug resistance.</td>
</tr>
<tr>
<td></td>
<td>• Increased exposure of other antiretroviral drugs (e.g., saquinavir) when used concomitantly with pantoprazole may increase toxicity of the antiretroviral drugs.</td>
</tr>
<tr>
<td></td>
<td>• There are other antiretroviral drugs which do not result in clinically relevant interactions with pantoprazole.</td>
</tr>
<tr>
<td>Intervention:</td>
<td>Rilpivirine-containing products: Concomitant use with PROTONIX I.V. is contraindicated [see Contraindications (4)]. See prescribing information.</td>
</tr>
<tr>
<td></td>
<td>Atazanavir: See prescribing information for atazanavir for dosing information.</td>
</tr>
<tr>
<td></td>
<td>Nelfinavir: Avoid concomitant use with PROTONIX I.V. See prescribing information for nelfinavir.</td>
</tr>
<tr>
<td></td>
<td>Saquinavir: See the prescribing information for saquinavir and monitor for potential saquinavir toxicities.</td>
</tr>
<tr>
<td></td>
<td>Other antiretrovirals: See prescribing information.</td>
</tr>
</tbody>
</table>

### Warfarin

<table>
<thead>
<tr>
<th>Clinical Impact:</th>
<th>Increased INR and prothrombin time in patients receiving PPIs, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention:</td>
<td>Monitor INR and prothrombin time. Dose adjustment of warfarin may be needed to maintain target INR range. See prescribing information for warfarin.</td>
</tr>
</tbody>
</table>
### Clopidogrel

**Clinical Impact:** Concomitant administration of pantoprazole and clopidogrel in healthy subjects had no clinically important effect on exposure to the active metabolite of clopidogrel or clopidogrel-induced platelet inhibition [see Clinical Pharmacology (12.3)].

**Intervention:** No dose adjustment of clopidogrel is necessary when administered with an approved dose of PROTONIX I.V..

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### Methotrexate

**Clinical Impact:** Concomitant use of PPIs with methotrexate (primarily at high dose) may elevate and prolong serum concentrations of methotrexate and/or its metabolite hydroxymethotrexate, possibly leading to methotrexate toxicities. No formal drug interaction studies of high-dose methotrexate with PPIs have been conducted [see Warnings and Precautions (5.14)].

**Intervention:** A temporary withdrawal of PROTONIX I.V. may be considered in some patients receiving high-dose methotrexate.

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### Drugs Dependent on Gastric pH for Absorption (e.g., iron salts, erlotinib, dasatinib, nilotinib, mycophenolate mofetil, ketoconazole/itraconazole)

**Clinical Impact:** Pantoprazole can reduce the absorption of other drugs due to its effect on reducing intragastric acidity.

**Intervention:** Mycophenolate mofetil (MMF): Co-administration of pantoprazole sodium in healthy subjects and in transplant patients receiving MMF has been reported to reduce the exposure to the active metabolite, mycophenolic acid (MPA), possibly due to a decrease in MMF solubility at an increased gastric pH [see Clinical Pharmacology (12.3)]. The clinical relevance of reduced MPA exposure on organ rejection has not been established in transplant patients receiving PROTONIX I.V. and MMF. Use PROTONIX I.V. with caution in transplant patients receiving MMF.

See the prescribing information for other drugs dependent on gastric pH for absorption.
Interactions with Investigations of Neuroendocrine Tumors

Clinical Impact: CgA levels increase secondary to PPI-induced decreases in gastric acidity. The increased CgA level may cause false positive results in diagnostic investigations for neuroendocrine tumors [see Warnings and Precautions (5.12), Clinical Pharmacology (12.2)].

Intervention: Temporarily stop PROTONIX I.V. treatment at least 14 days before assessing CgA levels and consider repeating the test if initial CgA levels are high. If serial tests are performed (e.g. for monitoring), the same commercial laboratory should be used for testing, as reference ranges between tests may vary.

False Positive Urine Tests for THC

Clinical Impact: There have been reports of false positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving PPIs [see Warnings and Precautions (5.13)].

Intervention: An alternative confirmatory method should be considered to verify positive results.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category C

Reproduction studies have been performed in rats at intravenous pantoprazole doses up to 20 mg/kg/day (4 times the recommended human dose based on body surface area) and rabbits at intravenous doses up to 15 mg/kg/day (6 times the recommended human dose based on body surface area) with administration of pantoprazole sodium during organogenesis in pregnant animals and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole.

A pre- and postnatal development toxicity study in rats with additional endpoints to evaluate the effect on bone development was performed with pantoprazole sodium. Oral pantoprazole doses of 5, 15, and 30 mg/kg/day (approximately 1, 3, and 6 times the human dose of 40 mg/day on a body surface area basis) were administered to pregnant females from gestation day (GD) 6 through lactation day (LD) 21. On postnatal day (PND 4) through PND 21, the pups were administered oral doses at 5, 15, and 30 mg/kg/day (approximately 1, 2.3, and 3.2 times the exposure (AUC) in humans at a dose of 40 mg). There were no drug-related findings in maternal animals. During the preweaning dosing phase (PND 4 to 21) of the pups, there were increased mortality and/or moribundity and decreased body weight and body weight gain at 5 mg/kg/day (approximately equal exposures (AUC) in humans receiving the 40 mg dose) and higher doses. On PND 21, decreased mean femur length and weight and changes in femur bone mass and...
geometry were observed in the offspring at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses. The femur findings included lower total area, bone mineral content and density, periosteal and endosteal circumference, and cross-sectional moment of inertia. There were no microscopic changes in the distal femur, proximal tibia, or stifle joints. Changes in bone parameters were partially reversible following a recovery period, with findings on PND 70 limited to lower femur metaphysis cortical/subcortical bone mineral density in female pups at 5 mg/kg/day (approximately equal exposures (AUC) in humans at the 40 mg dose) and higher doses.

There are no adequate and well-controlled studies in pregnant women. Advise pregnant women of the potential risk of fetal harm. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 of pantoprazole sodium. 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 sodium 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 I.V. have not been established in pediatric patients.

8.5 Geriatric Use

Of 286 patients in clinical studies of intravenous pantoprazole sodium in patients with GERD and a history of EE, 86 (43%) were 65 years of age and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience with oral pantoprazole sodium has not identified differences in responses.
between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

10 OVERDOSAGE

Experience in patients taking very high doses of pantoprazole (greater than 240 mg) is limited. Adverse reactions seen in spontaneous reports of overdose generally reflect the known safety profile of pantoprazole.

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

Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) 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® I.V. (pantoprazole sodium), a PPI, is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is C_{16}H_{14}F_{2}N_{3}NaO_{4}S, with a molecular weight of 405.4. The structural formula is:

Pantoprazole sodium is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium 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. The reconstituted solution of PROTONIX I.V. for injection is in the pH range 9.0 to 10.5.

PROTONIX I.V. is supplied for intravenous administration as a sterile, freeze-dried powder in a single-dose clear glass vial fitted with a rubber stopper and crimp seal. Each vial contains 40 mg pantoprazole (equivalent to 45.1 mg of pantoprazole sodium), edetate disodium (1 mg), and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pantoprazole is a 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

Antisecretory Activity

The magnitude and time course for inhibition of pentagastrin-stimulated acid output (PSAO) by single doses (20 to 120 mg) of PROTONIX I.V. were assessed in a single-dose, open-label, placebo-controlled, dose-response study. The results of this study are shown in Table 3. Healthy subjects received a continuous infusion for 25 hours of pentagastrin (PG) at 1 mcg/kg/h, a dose known to produce submaximal gastric acid secretion. The placebo group showed a sustained, continuous acid output for 25 hours, validating the reliability of the testing model. PROTONIX I.V. had an onset of antisecretory activity within 15 to 30 minutes of administration. Doses of 20 to 80 mg of PROTONIX I.V. substantially reduced the 24-hour cumulative PSAO in a dose-dependent manner, despite a short plasma elimination half-life. Complete suppression of PSAO was achieved with 80 mg within approximately 2 hours and no further significant suppression was seen with 120 mg. The duration of action of PROTONIX I.V. was 24 hours.

Table 3: Gastric Acid Output (mEq/hr, Mean ± SD) and Percent Inhibitiona (Mean ± SD) of Pentagastrin-Stimulated Acid Output Over 24 Hours Following a Single Dose of PROTONIX I.V. b in Healthy Subjects

<table>
<thead>
<tr>
<th>Treatment Dose</th>
<th>Acid Output</th>
<th>% Inhibition</th>
<th>Acid Output</th>
<th>% Inhibition</th>
<th>Acid Output</th>
<th>% Inhibition</th>
<th>Acid Output</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 mg (Placebo, n=4)</td>
<td>39 ± 21</td>
<td>NA</td>
<td>26 ± 14</td>
<td>NA</td>
<td>32 ± 20</td>
<td>NA</td>
<td>38 ± 24</td>
<td>NA</td>
</tr>
<tr>
<td>20 mg (n=4-6)</td>
<td>13 ± 18</td>
<td>47 ± 27</td>
<td>6 ± 8</td>
<td>83 ± 21</td>
<td>20 ± 10</td>
<td>54 ± 44</td>
<td>30 ± 23</td>
<td>45 ± 43</td>
</tr>
<tr>
<td>40 mg (n=8)</td>
<td>5 ± 5</td>
<td>82 ± 11</td>
<td>4 ± 4</td>
<td>90 ± 11</td>
<td>11 ± 10</td>
<td>81 ± 13</td>
<td>16 ± 12</td>
<td>52 ± 36</td>
</tr>
<tr>
<td>80 mg (n=8)</td>
<td>0.1 ± 0.2</td>
<td>96 ± 6</td>
<td>0.3 ± 0.4</td>
<td>99 ± 1</td>
<td>2 ± 2</td>
<td>90 ± 7</td>
<td>7 ± 4</td>
<td>63 ± 18</td>
</tr>
</tbody>
</table>

a: Compared to individual subject baseline prior to treatment with PROTONIX I.V. NA = not applicable.
b: Inhibition of gastric acid output and the percent inhibition of stimulated acid output in response to PROTONIX I.V. may be higher after repeated doses.

In one study of gastric pH in healthy subjects, PROTONIX was administered orally (40 mg enteric coated tablets) or PROTONIX I.V. (40 mg) once daily for 5 days and pH was measured for 24 hours following the fifth dose. The outcome measure was median percent of time that pH was ≥4 and the results were similar for intravenous and oral medications; however, the clinical significance of this parameter is unknown.

Serum Gastrin Effects

Serum gastrin concentrations were assessed in two placebo-controlled studies.

In a 5-day study of oral pantoprazole with 40 and 60 mg doses in healthy subjects, following the last dose on day 5, median 24-hour serum gastrin concentrations were elevated by 3- to 4-fold
compared to placebo in both 40 and 60 mg dose groups. However, by 24 hours following the last dose, median serum gastrin concentrations for both groups returned to normal levels.

In another placebo-controlled, 7-day study of 40 mg intravenous or oral pantoprazole in patients with GERD and a history of EE, the mean serum gastrin concentration increased approximately 50% from baseline and as compared with placebo, but remained within the normal range.

During 6 days of repeated administration of PROTONIX I.V. in patients with ZE Syndrome, consistent changes of serum gastrin concentrations from baseline were not observed.

**Enterochromaffin-Like (ECL) Cell Effects**

There are no data available on the effects of intravenous pantoprazole sodium on ECL cells.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to oral 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 PPIs. However, there were no observed elevations in serum gastrin following the administration of oral 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 oral pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery [see Nonclinical Toxicology (13.1)].

**Endocrine Effects**

In a clinical pharmacology study, pantoprazole 40 mg given orally once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, 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 pantoprazole 40 mg or 20 mg, there were no changes from baseline in overall levels of T3, T4, and TSH.

### 12.3 Pharmacokinetics

Pantoprazole peak serum concentration (C\text{max}) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following the administration of PROTONIX I.V., the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In CYP2C19 extensive metabolizers [see Clinical Pharmacology (12.5)] with normal liver function receiving a 40 mg dose of PROTONIX I.V. by constant rate over 15 minutes, the peak concentration (C\text{max}) is 5.52 ±1.42 mcg/mL and the total area under the plasma concentration versus time curve (AUC) is 5.4 ±1.5 mcg hr/mL. The total clearance is 7.6 to 14 L/h.

**Distribution**

The apparent volume of distribution of pantoprazole is approximately 11 to 23.6 L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.
Elimination

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. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3% of Caucasians and African-Americans and 17 to 23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5 to 10 hours, they still have minimal accumulation (23% or less) with once daily dosing.

Excretion

After administration of a single intravenous dose of $^{14}$C-labeled pantoprazole sodium to healthy, extensive CYP2C19 metabolizers, 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.

Specific Populations

Geriatric Patients

After repeated intravenous administration in elderly subjects (65 to 76 years of age), the AUC and elimination half-life values of pantoprazole were similar to those observed in younger subjects.

Male and Female Patients

After oral administration there was a modest increase in the AUC and $C_{\text{max}}$ of pantoprazole in women compared to men. However, weight-normalized clearance values are similar in women and men.

Patients with Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects.

Patients with Hepatic Impairment

In patients with mild to severe hepatic impairment (Child-Pugh Class A to C), maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects when pantoprazole sodium was administered orally. Although serum half-life values increased to 7 to 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. Oral pantoprazole doses higher than 40 mg per day have not been studied in hepatically impaired patients.
Drug Interaction Studies

Effect of Other Drugs on Pantoprazole

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.

Effect of Pantoprazole on Other Drugs

Clopidogrel

Clopidogrel is metabolized to its active metabolite in part by CYP2C19. In a crossover clinical study, 66 healthy subjects were administered clopidogrel (300 mg loading dose followed by 75 mg per day) alone and with oral pantoprazole (80 mg at the same time as clopidogrel) for 5 days. On Day 5, the mean AUC of the active metabolite of clopidogrel was reduced by approximately 14% (geometric mean ratio was 86%, with 90% CI of 79 to 93%) when pantoprazole sodium was coadministered with clopidogrel as compared to clopidogrel administered alone. Pharmacodynamic parameters were also measured and demonstrated that the change in inhibition of platelet aggregation (induced by 5 micromolar ADP) was correlated with the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

Mycophenolate Mofetil (MMF)

Administration of oral pantoprazole 40 mg twice daily for 4 days and a single 1000 mg dose of MMF approximately one hour after the last dose of pantoprazole to 12 healthy subjects in a cross-over study resulted in a 57% reduction in the \( C_{\text{max}} \) and 27% reduction in the AUC of MPA. Transplant patients receiving approximately 2000 mg per day of MMF (n=12) were compared to transplant patients receiving approximately the same dose of MMF and oral pantoprazole 40 mg per day (n=21). There was a 78% reduction in the \( C_{\text{max}} \) and a 45% reduction in the AUC of MPA in patients receiving both pantoprazole and MMF *[see Drug Interactions (7)]*.

Other Drugs

*In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, metoprolol, nifedipine, carbamazepeine, midazolam, clarithromycin, diclofenac, naproxen, piroxicam and oral contraceptives [levonorgestrel/ethinyl estradiol]). In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrene, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole.

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.
Antacids

There was also no interaction with concomitantly administered antacids.

12.5 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% or less) 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with pantoprazole 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 with 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 with 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 with 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus with 200 mg/kg/day. In the liver, treatment with 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment with 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 pantoprazole 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 with 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum with 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus with 200 mg/kg/day. In the liver, treatment with 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment with 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, B6C3F1 mice were treated orally with pantoprazole doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the gastric fundus, treatment with 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 pantoprazole 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 with 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment with 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).

14 CLINICAL STUDIES

14.1 Gastroesophageal Reflux Disease (GERD) Associated with a History of Erosive Esophagitis

A multicenter, double-blind, two-period placebo-controlled study was conducted to assess the ability of PROTONIX® I.V. to maintain gastric acid suppression in patients switched from PROTONIX Delayed-Release Tablets to PROTONIX I.V. GERD patients (n=65, 26 to 64 years; 35 female; 9 Black, 11 Hispanic, 44 White, 1 other) with a history of EE were randomized to receive either 20 or 40 mg of oral pantoprazole once per day for 10 days (period 1), and then were switched in period 2 to either daily PROTONIX I.V. or placebo for 7 days, matching their respective dose level from period 1. Patients were administered all test medication with a light meal. Maximum acid output (MAO) and basal acid output (BAO) were determined 24 hours following the last day of oral medication (day 10), the first day (day 1) of intravenous administration and the last day of intravenous administration (day 7). MAO was estimated from a 1 hour continuous collection of gastric contents following subcutaneous injection of 6.0 mcg/kg of pentagastrin.

This study demonstrated that, after 10 days of repeated oral administration followed by 7 days of intravenous administration, the oral and intravenous dosage forms of PROTONIX 40 mg are similar in their ability to suppress MAO and BAO in patients with GERD and a history of EE (see Table 4). Also, patients on oral PROTONIX who were switched to intravenous placebo experienced a significant increase in acid output within 48 hours of their last oral dose (see Table 4). However, at 48 hours after their last oral dose, patients treated with PROTONIX I.V. had a significantly lower mean basal acid output (see Table 4) than those treated with placebo.

Reference ID: 4274295
To evaluate the effectiveness of PROTONIX I.V. as an initial treatment to suppress gastric acid secretion, two studies were conducted.

Study 1 was a multicenter, double-blind, placebo-controlled, study of the pharmacodynamic effects of PROTONIX I.V. and PROTONIX Delayed-Release Tablets. Patients with GERD and a history of EE (n=78, 20 to 67 years; 39 females; 7 Black, 19 Hispanic, 52 White) were randomized to receive either 40 mg PROTONIX I.V., 40 mg PROTONIX Delayed-Release Tablets, or placebo once daily for 7 days. Following an overnight fast, test medication was administered and patients were given a light meal within 15 minutes. MAO and BAO were determined 24 hours following the last day of study medication. MAO was estimated from a 1 hour continuous collection of gastric contents following subcutaneous injection of 6.0 mcg/kg of pentagastrin to stimulate acid secretion. This study demonstrated that, after treatment for 7 days, patients treated with PROTONIX I.V. had a significantly lower MAO and BAO than those treated with placebo (p<0.001), and results were comparable to those of patients treated with PROTONIX Delayed-Release Tablets (see Table 5).

Table 4: Antisecretory Effects (mEq/h) of 40 mg PROTONIX I.V. and 40 mg PROTONIX Delayed-Release Tablets in GERD Patients with a History of EE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PROTONIX Delayed-Release Tablets DAY 10</th>
<th>PROTONIX I.V. DAY 7</th>
<th>Intravenous Placebo DAY 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean maximum acid output</td>
<td>6.49</td>
<td>6.62</td>
<td>29.19*</td>
</tr>
<tr>
<td>n=30</td>
<td></td>
<td>n=23</td>
<td>n=7</td>
</tr>
<tr>
<td>Mean basal acid output</td>
<td>0.80</td>
<td>0.53</td>
<td>4.14*</td>
</tr>
<tr>
<td>n=30</td>
<td></td>
<td>n=23</td>
<td>n=7</td>
</tr>
</tbody>
</table>

* p<0.0001 Significantly different from PROTONIX I.V.

Study 2 was a single-center, double-blind, parallel-group study to compare the clinical effects of PROTONIX I.V. and PROTONIX Delayed-Release Tablets. Patients (n=45, median age 56 years, 21 males and 24 females) with acute endoscopically proven reflux esophagitis (Savary/Miller Stage II or III) with at least 1 of 3 symptoms typical for reflux esophagitis (acid eructation, heartburn, or pain on swallowing) were randomized to receive either 40 mg

Table 5: Antisecretory Effects (mEq/h) of Initial Treatment with 40 mg PROTONIX I.V. and 40 mg PROTONIX Delayed-Release Tablets in GERD Patients with a History of EE

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PROTONIX I.V. DAY 7</th>
<th>PROTONIX Delayed-Release Tablets DAY 7</th>
<th>Placebo DAY 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum acid output (mean ± SD)</td>
<td>8.4 ± 5.9</td>
<td>6.3 ± 6.6</td>
<td>20.9 ± 14.5*</td>
</tr>
<tr>
<td>n=25</td>
<td></td>
<td>n=22</td>
<td>n=24</td>
</tr>
<tr>
<td>Basal acid output (mean ± SD)</td>
<td>0.4 ± 0.5</td>
<td>0.6 ± 0.8</td>
<td>2.8 ± 3.0*</td>
</tr>
<tr>
<td>n=25</td>
<td></td>
<td>n=22</td>
<td>n=23</td>
</tr>
</tbody>
</table>

* p<0.001 Significantly different from PROTONIX I.V.
PROTONIX I.V. or 40 mg PROTONIX Delayed-Release Tablets once daily for 5 days. After the initial 5 days, all patients were treated with 40 mg oral pantoprazole daily to complete a total of 8 weeks of treatment. Symptom relief was assessed by calculating the daily mean of the sums of the average scores for these 3 symptoms and the daily mean of the average score for each of the symptoms separately. There was no significant difference in symptom relief between PROTONIX I.V. and PROTONIX Delayed-Release Tablets within the first 5 days. A repeat endoscopy after 8 weeks of treatment revealed that 20 out of 23 (87%) patients treated with PROTONIX I.V. plus PROTONIX Delayed-Release Tablets and 19 out of 22 (86%) of the patients treated with PROTONIX Delayed-Release Tablets had endoscopically proven healing of their esophageal lesions.

Data comparing PROTONIX I.V. to other PPIs (oral or intravenous) or H2-receptor antagonists (oral or intravenous) are limited, and therefore, are inadequate to support any conclusions regarding comparative efficacy.

14.2 Pathological Hypersecretion Associated with Zollinger-Ellison Syndrome

Two studies measured the pharmacodynamic effects of 6 day treatment with PROTONIX I.V. in patients with ZE Syndrome (with and without multiple endocrine neoplasia type I). In one of these studies, an initial treatment with PROTONIX I.V. in 21 patients (29 to 75 years; 8 female; 4 Black, 1 Hispanic, 16 White) reduced acid output to the target level (10 mEq/h or less) and significantly reduced H+ concentration and the volume of gastric secretions; target levels were achieved within 45 minutes of drug administration.

In the other study of 14 patients (38 to 67 years; 5 female; 2 Black, 12 White) with ZE Syndrome, treatment was switched from an oral PPI to PROTONIX I.V. PROTONIX I.V. maintained or improved control of gastric acid secretion.

In both studies, total doses of 160 or 240 mg per day of PROTONIX I.V., administered in divided doses, maintained basal acid secretion below target levels in all patients. Target levels were 10 mEq/h in patients without prior gastric surgery, and 5 mEq/h in all patients with prior gastric acid-reducing surgery. Once gastric acid secretion was controlled, there was no evidence of tolerance during this 7 day study. Basal acid secretion was maintained below target levels for at least 24 hours in all patients and through the end of treatment in these studies (3 to 7 days) in all but 1 patient who required a dose adjustment guided by acid output measurements until acid control was achieved. In both studies, doses were adjusted to the individual patient need, but gastric acid secretion was controlled in greater than 80% of patients by a starting regimen of 80 mg every 12 hours.

16 HOW SUPPLIED/STORAGE AND HANDLING

PROTONIX® I.V. (pantoprazole sodium) is supplied in a single-dose vial as a white to off-white freeze-dried powder for reconstitution containing 40 mg of pantoprazole.

PROTONIX I.V. is available as follows:

<table>
<thead>
<tr>
<th>NDC Number</th>
<th>Strength</th>
<th>Package Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>NDC 0008-0923-51</td>
<td>40 mg pantoprazole</td>
<td>Single vial</td>
</tr>
<tr>
<td>NDC 0008-0923-55</td>
<td>40 mg pantoprazole</td>
<td>10 vials</td>
</tr>
<tr>
<td>NDC 0008-0923-60</td>
<td>40 mg pantoprazole</td>
<td>25 vials</td>
</tr>
</tbody>
</table>
Storage and Handling
Store PROTONIX I.V. 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].
Protect from light.

17 PATIENT COUNSELING INFORMATION

Adverse Reactions
Advise patients to report to their healthcare provider if they experience any signs or symptoms consistent with:

- Hypersensitivity and Severe Skin Reactions [see Warnings and Precautions (5.2)]
- Injection Site Reactions [see Warnings and Precautions (5.3)]
- Potential for Exacerbation of Zinc Deficiency [see Warnings and Precautions (5.4)]
- Acute Interstitial Nephritis [see Warnings and Precautions (5.5)]
- Clostridium difficile-Associated Diarrhea [see Warnings and Precautions (5.6)]
- Bone Fracture [see Warnings and Precautions (5.7)]
- Cutaneous and Systemic Lupus Erythematosus [see Warnings and Precautions (5.8)]
- Hepatic Effects [see Warnings and Precautions (5.9)]
- Hypomagnesemia [see Warnings and Precautions (5.10)]

Drug Interactions
Instruct patients to inform their healthcare provider of any other medications they are currently taking, including rilpivirine-containing products [Contraindications (4)] and high dose methotrexate [Warnings and Precautions (5.14)].

Pregnancy
Inform female patients of reproductive potential that PROTONIX I.V. may cause fetal harm and to inform their prescriber of a known or suspected pregnancy [see Use in Specific Populations (8.1)].

This product’s label may have been updated. For current full prescribing information, please visit www.pfizer.com.

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LAB-0462-17.0