

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

PROTONIX® I.V. (pantoprazole sodium) for injection, for intravenous use
Initial U.S. approval: 2000

----- **RECENT MAJOR CHANGES** -----

Warnings and Precautions, Concomitant use of Protonix with Methotrexate (5.9) 5/2012

----- **INDICATIONS AND USAGE** -----

PROTONIX is a proton pump inhibitor indicated for the following:

- Short-term Treatment (7 to 10 days) of Gastroesophageal Reflux Disease (GERD) Associated With a History of Erosive Esophagitis (1.1)
- Pathological Hypersecretion Conditions Including Zollinger-Ellison Syndrome (1.2)

----- **DOSAGE AND ADMINISTRATION** -----

- The recommended adult dose is 40 mg pantoprazole given once daily by intravenous infusion for 7 to 10 days. (2.1)

----- **DOSAGE FORMS AND STRENGTHS** -----

- PROTONIX® I.V. (pantoprazole sodium) for Injection: 40 mg pantoprazole (3)

----- **CONTRAINDICATIONS** -----

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

----- **WARNINGS AND PRECAUTIONS** -----

- Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy (5.1)
- Anaphylaxis has been reported with use of intravenous pantoprazole (5.2)
- Thrombophlebitis is associated with the administration of intravenous pantoprazole (5.3)
- Zinc supplementation should be considered in patients treated with PROTONIX I.V. for Injection who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously (5.4)
- Bone Fracture: PPI therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist or spine after long term and multiple daily dose (5.5)
- Hypomagnesemia has been reported rarely with prolonged treatment with PPIs (5.7)

----- **ADVERSE REACTIONS** -----

The most frequently occurring adverse reactions are as follows:

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

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** -----

- Do not co-administer with atazanavir or nelfinavir (7.1)
- Concomitant warfarin use may require monitoring (7.2)
- May interfere with the absorption of drugs where gastric pH is important for bioavailability (7.3)
- May produce false-positive urine screen for THC (7.4)
- Methotrexate: Protonix may increase serum level of methotrexate (7.6)

See 17 for PATIENT COUNSELING INFORMATION

Revised: 05/2012

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Gastroesophageal Reflux Disease Associated with a History of Erosive Esophagitis

PROTONIX I.V. for Injection is indicated for short-term treatment (7 to 10 days) of adult patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis.

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

1.2 Pathological Hypersecretion Including Zollinger-Ellison Syndrome

PROTONIX I.V. for Injection is indicated for the treatment of pathological hypersecretory conditions including Zollinger-Ellison Syndrome in adults.

2 DOSAGE AND ADMINISTRATION

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to and during administration whenever solution and container permit.

Parenteral routes of administration other than intravenous are not recommended.

PROTONIX I.V. for Injection may be administered intravenously through a dedicated line or through a Y-site. The intravenous line should be flushed before and after administration of PROTONIX I.V. for Injection 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. for Injection 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. for Injection. PROTONIX I.V. for Injection may not be compatible with products containing zinc. When PROTONIX I.V. for Injection is administered through a Y-site, immediately stop use if precipitation or discoloration occurs.

2.1 Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

Recommended Dosage

The recommended adult dose is 40 mg pantoprazole given once daily by intravenous infusion for 7 to 10 days.

Treatment with PROTONIX[®] I.V. (pantoprazole sodium) for Injection should be discontinued as soon as the patient is able to receive treatment with PROTONIX Delayed-Release Tablets or Oral Suspension.

Administration and Preparation Instructions

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.

Fifteen Minute Infusion

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted (admixed) 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. 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.

PROTONIX I.V. for Injection admixtures should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Two Minute Infusion

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, to a final concentration of approximately 4 mg/mL. 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. PROTONIX I.V. for Injection should be administered intravenously over a period of at least 2 minutes.

2.2 Pathological Hypersecretion Including Zollinger-Ellison Syndrome

Recommended Dosage

The dosage of PROTONIX I.V. for Injection in patients with pathological hypersecretory conditions including Zollinger-Ellison Syndrome varies with individual patients. The recommended adult dosage 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 Zollinger-Ellison Syndrome may be vulnerable to serious clinical complications of increased acid production even after a short period of loss of effective inhibition.

Administration and Preparation Instructions

Fifteen Minute Infusion

Each vial of PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be combined and further diluted (admixed) 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. 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.

PROTONIX I.V. for Injection should be administered intravenously over a period of approximately 15 minutes at a rate of approximately 7 mL/min.

Two minute Infusion

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, per vial to a final concentration of approximately 4 mg/mL. 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. The total volume from both vials should be administered intravenously over a period of at least 2 minutes.

3 DOSAGE FORMS AND STRENGTHS

PROTONIX[®] I.V. (pantoprazole sodium) for Injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial.

4 CONTRAINDICATIONS

PROTONIX is contraindicated in patients with known hypersensitivity reactions including anaphylaxis to the formulation [*see Warnings and Precautions (5.2)*] or any substituted benzimidazole.

5 WARNINGS AND PRECAUTIONS

5.1 Implications of Symptomatic Response

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

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 intravenous pantoprazole. These may require emergency medical treatment [*see Adverse Reactions (6.2)*].

5.3 Injection Site Reactions

Thrombophlebitis was associated with the administration of intravenous pantoprazole.

5.4 Potential for Exacerbation of Zinc Deficiency

Protonix 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. for Injection who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously.

5.5 Bone Fracture

Several published observational studies suggest that proton pump inhibitor (PPI) therapy may be associated with an increased risk for osteoporosis-related fractures of the hip, wrist, or spine. The risk of fracture was increased in patients who received high-dose, defined as multiple daily doses, and long-term PPI therapy (a year or longer). Patients should use the lowest dose and

shortest duration of PPI therapy appropriate to the condition being treated. Patients at risk for osteoporosis-related fractures should be managed according to established treatment guidelines. (See *Dosage and Administration and Adverse Reactions* sections).

5.6 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 intravenous pantoprazole is unknown. (See *Adverse Reactions*).

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 Interference with Urine Screen for THC

May produce false-positive urine screen for THC (tetrahydrocannabinol). [See *Drug Interactions* (7.4)].

5.9 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)]

6 ADVERSE REACTIONS

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

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.

Gastroesophageal Reflux Disease (GERD)

Safety in nine randomized comparative US clinical trials in patients with GERD included 1,473 patients on oral pantoprazole (20 mg or 40 mg), 299 patients on an H₂-receptor antagonist, 46

patients on another proton pump inhibitor, 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 I.V. pantoprazole 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 I.V. pantoprazole.

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

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

Additional adverse reactions that were reported for PROTONIX in US clinical trials with a frequency of $\leq 2\%$ 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 Syndrome

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

6.2 Postmarketing Experience

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

These adverse reactions are listed below by body system:

General Disorders and Administration Conditions: asthenia, fatigue, malaise

Immune System Disorders: anaphylaxis (including anaphylactic shock)

Investigations: weight changes

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

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

7 DRUG INTERACTIONS

7.1 Interference with Antiretroviral Therapy

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

7.2 Coumarin Anticoagulants

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

7.3 Clopidogrel

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)]. No dose adjustment of clopidogrel is necessary when administered with an approved dose of Protonix.

7.4 Drugs for which Gastric pH Can Affect Bioavailability

Pantoprazole causes long-lasting inhibition of gastric acid secretion, therefore pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their

bioavailability (e.g., ketoconazole, ampicillin esters, iron salts, and digoxin).

7.5 False Positive Urine Tests for THC

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

7.6 Methotrexate

Case reports, published population pharmacokinetic studies, and retrospective analyses suggest that concomitant administration of PPIs and methotrexate (primarily at high dose; see methotrexate prescribing information) may elevate and prolong serum levels of methotrexate and/or its metabolite hydroxymethotrexate. However, no formal drug interaction studies of methotrexate with PPIs have been conducted [*see Warnings and Precautions (5.9)*].

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness of PROTONIX I.V. in pediatric patients have not been established.

8.5 Geriatric Use

No age-related differences in the safety profile of intravenous pantoprazole were seen in international trials involving 86 elderly (≥ 65 years old) and 200 younger (< 65 years old) patients with erosive esophagitis associated with GERD. Erosive esophagitis healing rates in the

107 elderly patients (≥ 65 years old) treated with oral pantoprazole in U.S. clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age.

8.6 Gender

No gender-related differences in the safety profile of intravenous pantoprazole were seen in international trials involving 166 men and 120 women with erosive esophagitis associated with GERD. Erosive esophagitis healing rates in the 221 women treated with oral pantoprazole in U.S. clinical trials were similar to those found in men. The incidence rates of adverse reactions were also similar for men and women.

8.7 Hepatic Impairment

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

10 OVERDOSAGE

Experience in patients taking very high doses of pantoprazole (> 240 mg) is limited. Adverse events 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.

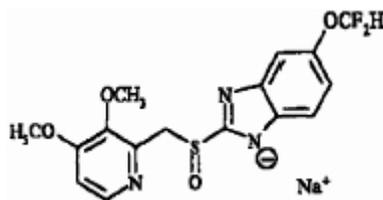
Single intravenous doses of pantoprazole at 378, 230, and 266 mg/kg (38, 46, and 177 times the recommended human dose based on body surface area) were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

11 DESCRIPTION

Therapeutic class: Proton Pump Inhibitor (PPI)

Route of administration: For Intravenous use only

The active ingredient in PROTONIX[®] I.V. (intravenous pantoprazole sodium) for Injection 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 $C_{16}H_{14}F_2N_3NaO_4S$, 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. for Injection is supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing pantoprazole sodium, equivalent to 40 mg of pantoprazole, edetate disodium (1 mg), and sodium hydroxide to adjust pH.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

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

12.2 Pharmacodynamics

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. for Injection were assessed in a single-dose, open-label, placebo-controlled, dose-response study. The results of this study are shown in Table 2. 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. for Injection had an onset of antisecretory activity within 15 to 30 minutes of administration. Doses of 20 to 80 mg of PROTONIX I.V. for Injection 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. for Injection was 24 hours.

Table 2: Gastric Acid Output (mEq/hr, Mean ± SD) and Percent Inhibition^a (Mean ± SD) of Pentagastrin-Stimulated Acid Output Over 24 Hours Following a Single Dose of PROTONIX I.V. for Injection^b in Healthy Subjects

Treatment Dose	-----2 hours-----		-----4 hours-----		-----12 hours-----		-----24 hours-----	
	Acid Output	% Inhibition	Acid Output	% Inhibition	Acid Output	% Inhibition	Acid Output	% Inhibition
0 mg (Placebo, n=4)	39 ± 21	NA	26 ± 14	NA	32 ± 20	NA	38 ± 24	NA
20mg	13 ±	47 ± 27	6 ± 8	83 ± 21	20 ±	54 ± 44	30 ±	45 ± 43

Table 2: Gastric Acid Output (mEq/hr, Mean ± SD) and Percent Inhibition^a (Mean ± SD) of Pentagastrin-Stimulated Acid Output Over 24 Hours Following a Single Dose of PROTONIX I.V. for Injection^b in Healthy Subjects

Treatment Dose	-----2 hours-----		-----4 hours-----		-----12 hours-----		-----24 hours-----	
	Acid Output	% Inhibition	Acid Output	% Inhibition	Acid Output	% Inhibition	Acid Output	% Inhibition
(n=4-6)	18				20		23	
40 mg (n=8)	5 ± 5	82 ± 11	4 ± 4	90 ± 11	11 ± 10	81 ± 13	16 ± 12	52 ± 36
80 mg (n=8)	0.1 ± 0.2	96 ± 6	0.3 ± 0.4	99 ± 1	2 ± 2	90 ± 7	7 ± 4	63 ± 18

a: Compared to individual subject baseline prior to treatment with PROTONIX I.V. for Injection. NA = not applicable.

b: Inhibition of gastric acid output and the percent inhibition of stimulated acid output in response to PROTONIX I.V. for Injection may be higher after repeated doses.

In one study of gastric pH in healthy subjects, pantoprazole was administered orally (40 mg enteric coated tablets) or intravenously (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 3-4 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 erosive esophagitis, 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. for Injection in patients with Zollinger-Ellison 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 on ECL cells.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin concentrations. The high density of ECL cells in the rat

stomach makes this species highly susceptible to the proliferative effects of elevated gastrin concentrations produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery [see *Nonclinical Toxicology (13.1)*].

12.3 Pharmacokinetics

Pantoprazole peak serum concentration (C_{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. for Injection, 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. for Injection by constant rate over 15 minutes, the peak concentration (C_{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 7.6-14.0 L/h.

Distribution

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

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g., 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values from 3.5 to 10.0 hours, they still have minimal accumulation ($\leq 23\%$) with once daily dosing.

Excretion

After administration of a single intravenous dose of ^{14}C -labeled pantoprazole 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.

Geriatric

After repeated I.V. administration in elderly subjects (65 to 76 years of age), pantoprazole AUC and elimination half-life values were similar to those observed in younger subjects. No dosage adjustment is recommended for elderly patients.

Gender

After oral administration there is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is warranted based on gender.

Renal Impairment

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

Hepatic Impairment

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

Drug-Drug Interactions

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

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 μ M ADP) was correlated with the change in the exposure to clopidogrel active metabolite. The clinical significance of this finding is not clear.

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, warfarin, metoprolol, nifedipine, carbamazepine, midazolam, clarithromycin, naproxen, piroxicam and oral contraceptives [levonorgestrel/ethinyl estradiol]). Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole.

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

There was also no interaction with concomitantly administered antacids.

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

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

Other Effects

In a clinical pharmacology study, 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.

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 ($\leq 23\%$) with once-daily dosing. For adult patients who are CYP2C19 poor metabolizers, no dosage adjustment is needed.

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface area basis of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about

10 and 40 times the recommended human dose on a body surface area basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

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

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

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

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

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

13.2 Animal Toxicology and/or Pharmacology

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

repeated-dose studies in rats and/or dogs. Full to partial recovery of these effects were noted in animals of both age groups following a recovery period.

Reproductive Toxicology Studies

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

14 CLINICAL STUDIES

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. (pantoprazole sodium) for Injection to maintain gastric acid suppression in patients switched from the oral dosage form of pantoprazole to the intravenous dosage form. Gastroesophageal reflux disease (GERD) patients (n=65, 26 to 64 years; 35 female; 9 Black, 11 Hispanic, 44 White, 1 other) with a history of erosive esophagitis 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 intravenous pantoprazole 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 µg/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 erosive esophagitis (see Table 3). 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 3). However, at 48 hours after their last oral dose, patients treated with PROTONIX I.V. for Injection had a significantly lower mean basal acid output (see Table 3) than those treated with placebo.

Table 3: ANTISECRETORY EFFECTS (mEq/h) OF 40 mg PROTONIX I.V. for INJECTION AND 40 mg ORAL PROTONIX IN GERD PATIENTS WITH A HISTORY OF EROSIIVE ESOPHAGITIS

Parameter	PROTONIX Delayed-Release Tablets DAY 10	PROTONIX I.V. for Injection DAY 7	Placebo I.V. DAY 7
Mean maximum acid output	6.49 n=30	6.62 n=23	29.19* n=7
Mean basal acid output	0.80 n=30	0.53 n=23	4.14* n=7

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

To evaluate the effectiveness of PROTONIX I.V. (pantoprazole sodium) for Injection 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. for Injection and oral PROTONIX. Patients with GERD and a history of erosive esophagitis (n=78, 20-67 years; 39 females; 7 Black, 19 Hispanic, 52 White) were randomized to receive either 40 mg intravenous pantoprazole, 40 mg oral pantoprazole, 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 µg/kg of pentagastrin to stimulate acid secretion. This study demonstrated that, after treatment for 7 days, patients treated with PROTONIX I.V. for Injection 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 oral PROTONIX (see Table 4).

Table 4: ANTISECRETORY EFFECTS (mEq/h) OF INITIAL TREATMENT WITH 40 mg PROTONIX I.V. for INJECTION AND 40 mg ORAL PROTONIX IN GERD PATIENTS WITH A HISTORY OF EROSIIVE ESOPHAGITIS

Parameter	PROTONIX I.V. for Injection DAY 7	PROTONIX Delayed-Release Tablets DAY 7	Placebo DAY 7
Maximum acid output (mean ± SD)	8.4 ± 5.9 n=25	6.3 ± 6.6 n=22	20.9 ± 14.5* n=24
Basal acid output (mean ± SD)	0.4 ± 0.5 n=25	0.6 ± 0.8 n=22	2.8 ± 3.0* n=23

* p<0.001 Significantly different from PROTONIX I.V. for Injection.

Study 2 was a single-center, double-blind, parallel-group study to compare the clinical effects of PROTONIX I.V. for Injection and oral PROTONIX. 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 intravenous pantoprazole or 40 mg oral pantoprazole 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 oral PROTONIX therapy within the first 5 days. A repeat endoscopy after 8 weeks of treatment revealed that 20 out of 23 (87%) of the PROTONIX I.V. plus oral PROTONIX patients and 19 out of 22 (86%) of the oral PROTONIX patients had endoscopically proven healing of their esophageal lesions.

Data comparing PROTONIX I.V. for Injection to other proton pump inhibitors (oral or I.V.) or H₂ receptor antagonists (oral or I.V.) 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. for Injection in patients with Zollinger-Ellison Syndrome (with and without multiple endocrine neoplasia type I). In one of these studies, an initial treatment with PROTONIX I.V. for Injection 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) 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 Zollinger-Ellison Syndrome, treatment was switched from an oral proton pump inhibitor to PROTONIX I.V. for Injection. PROTONIX I.V. for Injection maintained or improved control of gastric acid secretion.

In both studies, PROTONIX I.V. for Injection 160 or 240 mg per day 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 q12h.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

PROTONIX® I.V. (pantoprazole sodium) for Injection is supplied as a freeze-dried powder containing 40 mg of pantoprazole per vial.

PROTONIX I.V. for Injection is available as follows:

NDC 0008-0923-55 – Package of 10. Each vial (NDC 0008-0923-51) contains PROTONIX I.V. for Injection (each vial containing 40 mg pantoprazole).

NDC 0008-0923-60 – Package of 25. Each vial (NDC 0008-0923-51) contains PROTONIX I.V. for Injection (each vial containing 40 mg pantoprazole).

Storage and Handling

Store PROTONIX I.V. for Injection vials at 20° - 25°C (68° - 77°F); excursions permitted to 15° - 30°C (59° - 86°F). [*See USP Controlled Room Temperature.*]

Protect from light. The reconstituted product should not be frozen.

17 PATIENT COUNSELING INFORMATION

Inform patients that the most frequently occurring adverse reactions in US clinical trials for adults are headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia.

Patients should be instructed to inform their healthcare provider if they develop any unusual symptom, or if any known symptom persists or worsens. Patients should be instructed to inform their healthcare provider of any other medications they are currently taking, including over-the-counter medications, as well as allergies to any medications.



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