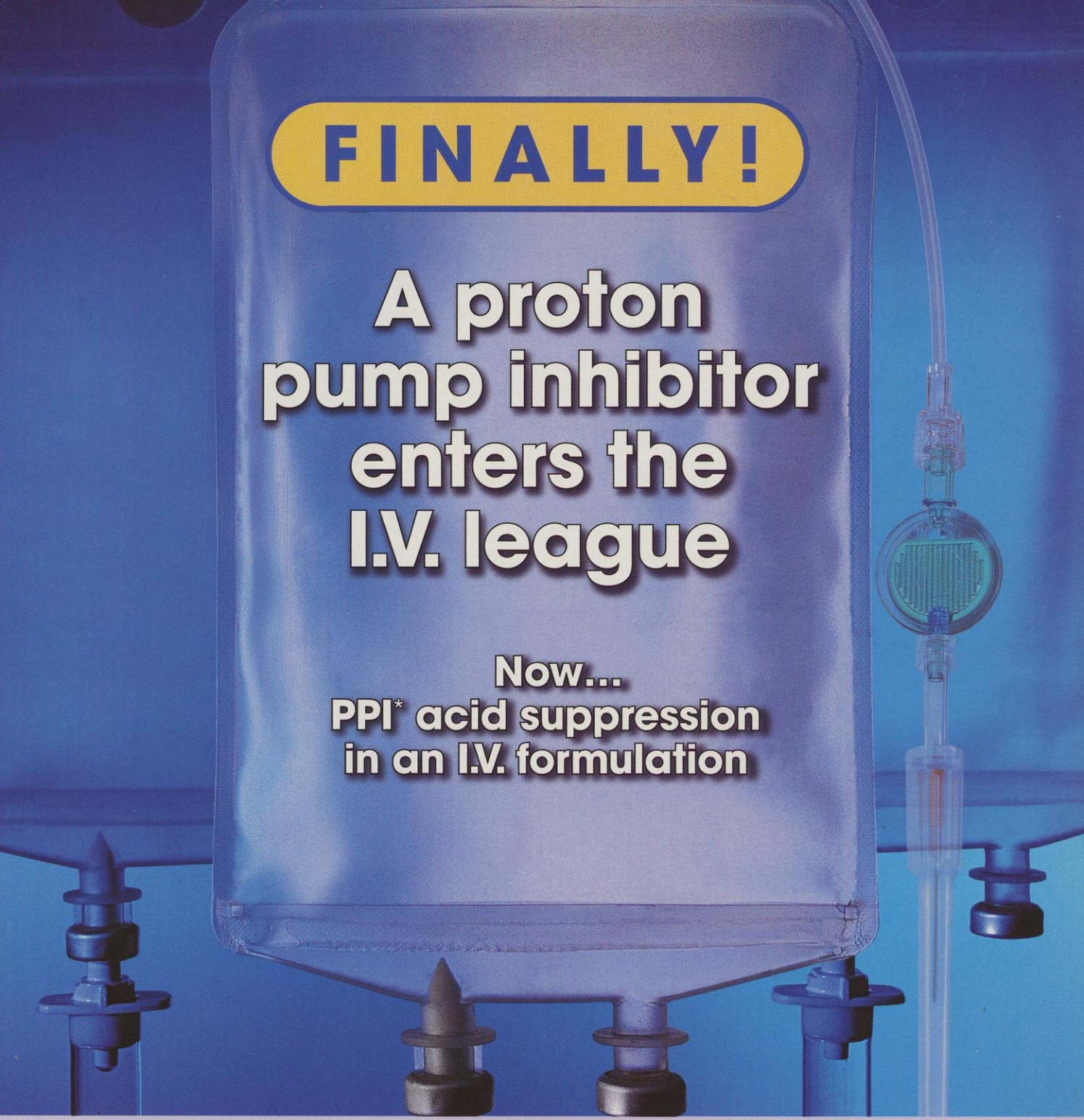
Protonix advertisement.

[s.l.]: [s.n.], 2000



PROTONIX I.V. is indicated for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), **as an alternative to oral therapy in patients who are unable to continue taking PROTONIX Delayed-Release Tablets.** Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated.

The most frequently reported adverse events with PROTONIX I.V. are abdominal pain, chest pain, rash, and pruritus. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX I.V. is contraindicated in patients with known hypersensitivity to any component of the formulation. Treatment with PROTONIX I.V. should be discontinued as soon as the patient is able to be treated with PROTONIX Delayed-Release Tablets.

*PPI (proton pump inhibitor).

NEW

PROTONIX® I.V.

(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

Please see brief summary of Prescribing Information on reverse side of this advertisement.

NEW PROTONIX® I.V.

(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

See package insert for full prescribing information.

INDICATIONS AND USAGE

Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), **as an alternative in patients who are unable to continue taking PROTONIX (pantoprazole sodium) Delayed-Release Tablets.** Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated.

CONTRAINDICATIONS

Patients with known hypersensitivity to the formulation.

PRECAUTIONS

General

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

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (<21%), when dosed as recommended at 40 mg once daily, needs to be weighed against the potential for reduced acid control when decreasing the dose or altering the dosing regimen in these patients.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets.

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 (a CYP3A4 substrate), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *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 and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

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 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.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month oral toxicity studies.

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 combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

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.

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

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

Use in Elderly

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 GERD. Erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with oral pantoprazole in US 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. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of oral pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS

Safety Experience with Intravenous Pantoprazole

Intravenous pantoprazole has been well tolerated in clinical trials of GERD patients and healthy subjects. A double-blind placebo controlled study in the U.S. evaluated the effect of PROTONIX I.V. for Injection on pentagastrin-stimulated acid secretion in 65 GERD patients. Treatment-emergent events considered possibly, probably or definitely drug-related that were reported by 2 or more patients (≥ 4%) taking PROTONIX I.V. (pantoprazole sodium) for Injection (n=50) and by 0% of patients taking placebo (n=15) were: abdominal pain (12%), chest pain (6%), rash (6%), and pruritus (4%). Additional adverse experiences occurring in >1% of GERD patients treated with intravenous pantoprazole (n=412) in domestic (n=50) or international (n=362) clinical trials are shown below by body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS A WHOLE: headache, injection site reaction.

DIGESTIVE SYSTEM: dyspepsia, nausea, diarrhea, vomiting.

NERVOUS SYSTEM: dizziness.

RESPIRATORY SYSTEM: rhinitis.

The safety of intravenous pantoprazole has also been evaluated during international clinical trials conducted in over 300 critically ill patients. The safety profile of intravenous pantoprazole was similar to that of oral pantoprazole with the exception of injection site reactions including injection site inflammation, thrombophlebitis, hemorrhage, and abscess. Head-to-head comparative studies between PROTONIX I.V. for Injection and oral PROTONIX, other proton pump inhibitors (oral or I.V.) or H2 receptor antagonists (oral or I.V.) have been limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

Safety Experience with Oral Pantoprazole

In short-term clinical trials in GERD patients treated with oral pantoprazole, the following adverse events, regardless of causality, occurred at a rate of ≥ 1%.

BODY AS A WHOLE: headache, asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain.

CARDIOVASCULAR SYSTEM: migraine.

DIGESTIVE SYSTEM: diarrhea, flatulence, abdominal pain, eructation, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting.

HEPATO-BILIARY SYSTEM: liver function tests abnormal, SGPT increased.

METABOLIC AND NUTRITIONAL: hyperglycemia, hyperlipidemia.

MUSCULOSKELETAL SYSTEM: arthralgia.

NERVOUS SYSTEM: insomnia, anxiety, dizziness, hypertonia.

RESPIRATORY SYSTEM: bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

SKIN AND APPENDAGES: rash.

UROGENITAL SYSTEM: urinary frequency, and urinary tract infection.

Additional adverse experiences occurring in <1% of GERD patients receiving oral pantoprazole based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with postmarketing use of intravenous or oral pantoprazole, including anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); pancreatitis; jaundice; confusion; hypokinesia; speech disorder; increased salivation; vertigo; nausea; and tinnitus.

In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In U.S. and international GERD clinical trials, the overall percentages of transaminase elevations did not increase during treatment with intravenous pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two U.S. controlled trials of oral pantoprazole in patients with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of oral pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

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.

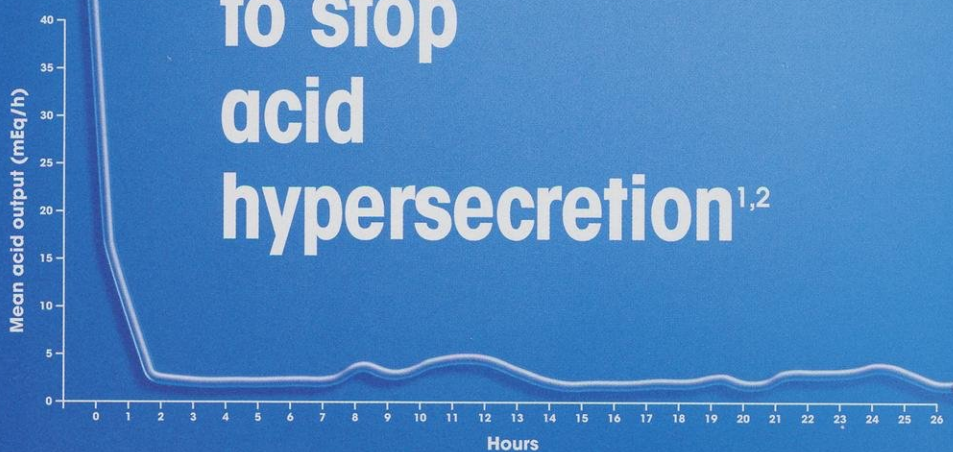
℞ only

US Patent No. 4,758,579

Manufactured for Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101
under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany
This Brief Summary is based on CI 6005-2 4/27/01

Indicated for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions.

Strong enough to stop acid hypersecretion[1,2]



n = 17/21 PROTONIX I.V. 80 mg q12h (Four patients required 240 mg/day)

PROTONIX® I.V.
(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

In clinical trials, the most frequently reported adverse events with PROTONIX I.V. were injection site reactions (including thrombophlebitis and abscess), headache, diarrhea, nausea, and dyspepsia. PROTONIX I.V. is contraindicated in patients with known hypersensitivity to any component of the formulation. Anaphylaxis has been reported. Treatment with PROTONIX I.V. should be discontinued as soon as the patient is able to be treated with PROTONIX Delayed-Release Tablets. **Please see brief summary of Prescribing Information on adjacent page.**

PROTONIX® I.V.

(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

See package insert for full prescribing information.

INDICATIONS AND USAGE

Treatment of Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

Short-term treatment (7 to 10 days) of patients having gastroesophageal reflux disease (GERD) with a history of erosive esophagitis, **as an alternative to oral therapy in patients who are unable to continue taking PROTONIX (pantoprazole sodium) Delayed-Release Tablets.** Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment of patients having GERD with a history of erosive esophagitis have not been demonstrated.

Pathological Hypersecretion Associated With Zollinger-Ellison Syndrome

Treatment of pathological hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions.

CONTRAINDICATIONS

Patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

Immediate hypersensitivity reactions: Anaphylaxis has been reported with use of intravenous pantoprazole. This may require emergency medical treatment.

Injection site reactions: Thrombophlebitis was associated with the administration of intravenous pantoprazole.

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** section.)

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

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets.

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 (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *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, and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are coadministered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, caffeine, metronidazole, and amoxicillin had no clinically relevant interactions with pantoprazole. 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.

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

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.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month oral toxicity studies.

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.

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

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

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 events were also similar between men and women.

Use in Elderly

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.

Laboratory Tests

There have been reports of false-positive urine screening tests for tetrahydrocannabinol (THC) in patients receiving pantoprazole.

ADVERSE REACTIONS

Safety Experience With Intravenous Pantoprazole

Intravenous pantoprazole has been studied in clinical trials in several populations including patients having GERD with a history of erosive esophagitis, patients with Zollinger-Ellison syndrome, and healthy subjects. Adverse experiences occurring in >1% of patients treated with intravenous pantoprazole (n=714) in domestic and international clinical trials are shown below by body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abdominal pain, headache, injection site reaction (including thrombophlebitis and abscess).

DIGESTIVE SYSTEM: constipation, dyspepsia, nausea, diarrhea.

NERVOUS SYSTEM: insomnia.

RESPIRATORY SYSTEM: rhinitis.

Head-to-head comparative studies between PROTONIX I.V. for Injection and oral PROTONIX, other proton pump inhibitors (oral or I.V.), or H2 receptor antagonists (oral or I.V.) have been limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

Safety Experience With Oral Pantoprazole

In short-term clinical trials in patients with erosive esophagitis associated with GERD treated with oral pantoprazole, the following adverse events, regardless of causality, occurred at a rate of ≥1%.

BODY AS A WHOLE: headache, asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain.

CARDIOVASCULAR SYSTEM: migraine.

DIGESTIVE SYSTEM: diarrhea, flatulence, abdominal pain, eructation, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting.

HEPATO-BILIARY SYSTEM: liver function tests abnormal, SGPT increased.

METABOLIC AND NUTRITIONAL: hyperglycemia, hyperlipidemia.

MUSCULOSKELETAL SYSTEM: arthralgia.

NERVOUS SYSTEM: insomnia, anxiety, dizziness, hypertonia.

RESPIRATORY SYSTEM: bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

SKIN AND APPENDAGES: rash.

UROGENITAL SYSTEM: urinary frequency, urinary tract infection.

Additional adverse experiences occurring in <1% of patients with erosive esophagitis associated with GERD receiving oral pantoprazole based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction.

CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

The postmarketing safety profile of intravenous pantoprazole (from an estimate of over 700,000 patients) is not substantially different from that of oral pantoprazole (described below).

There have been spontaneous reports of adverse events with postmarketing use of intravenous or oral pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis; pancytopenia; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In U.S. clinical trials of patients having GERD with a history of erosive esophagitis and international clinical trials of patients with erosive esophagitis associated with GERD, the overall percentages of transaminase elevations did not increase during treatment with intravenous pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two U.S. controlled trials of oral pantoprazole in patients with erosive esophagitis associated with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Experience in patients taking very high doses of pantoprazole is limited. There have been spontaneous reports of overdosage with pantoprazole, including a suicide in which pantoprazole 560 mg and undetermined amounts of chloroquine and zopiclone were also ingested. There have also been spontaneous reports of patients taking similar amounts of pantoprazole (400 and 600 mg) with no adverse effects.

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.

DOSAGE AND ADMINISTRATION

PROTONIX I.V. for Injection admixtures should be administered intravenously through a dedicated line, using the in-line filter provided. **The filter must be used** to remove the precipitate that may form when the reconstituted drug product is mixed with I.V. solutions. Studies have shown that filtration does not alter the amount of drug that is available for administration. If administration through a Y-site is desirable, the in-line filter must be positioned below the Y-site that is closest to the patient. 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. PROTONIX I.V. for Injection should not be simultaneously administered through the same line with other intravenous solutions.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets. Also, data on safe and effective dosing for conditions other than those described in **INDICATIONS AND USAGE,** 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.

Parenteral routes of administration other than intravenous are not recommended.

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

Treatment of Gastroesophageal Reflux Disease Associated With a History of Erosive Esophagitis

The recommended adult dose, **as an alternative to continued oral therapy**, is 40-mg pantoprazole given once daily by intravenous infusion for 7 to 10 days. Safety and efficacy of PROTONIX I.V. for Injection as a treatment of patients having GERD with a history of erosive esophagitis for more than 10 days have not been demonstrated (see **INDICATIONS AND USAGE**).

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 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution needs 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 not greater than 3 mg/min (7 mL/min).

Pathological Hypersecretion Associated With Zollinger-Ellison Syndrome

The dosage of PROTONIX I.V. for Injection in patients with pathological hypersecretory conditions associated with Zollinger-Ellison syndrome or other neoplastic conditions varies with individual patients. The recommended adult dosage is 80 mg q12h. 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 q8h 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** section of full Prescribing Information.) Transition from oral to I.V. and from I.V. 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.

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 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 12 hours at room temperature prior to intravenous infusion. Neither the reconstituted solution nor the admixed solution needs to be protected from light.

PROTONIX I.V. for Injection should be administered intravenously over a period of approximately 15 minutes at a rate not greater than 6 mg/min (7 mL/min).

℞ only

US Patent No. 4,758,579

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under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on CI 6005-5 2/11/02.

References: 1. Data on file, Wyeth Pharmaceuticals. **2.** Lew EA, Pisegna JR, Starr JA, et al. Intravenous pantoprazole rapidly controls gastric acid hypersecretion in patients with Zollinger-Ellison syndrome. *Gastroenterology*. 2000;118:696-704.

Nighttime heartburn: a rude awakening

PROTONIX® tames erosive GERD night after night

PROTONIX is indicated for the treatment and maintenance of healing of erosive esophagitis with associated gastroesophageal reflux disease (GERD) symptoms. Controlled studies did not extend beyond 12 months.

The most frequently reported adverse events with PROTONIX Delayed-Release Tablets are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. **Please see brief summary of Prescribing Information on adjacent page.**

ONCE-A-DAY

PROTONIX® (Pantoprazole Sodium) Delayed Release Tablets **40mg**

Makes erosive GERD nights *good* nights™

PROTONIX® 40mg

(Pantoprazole Sodium) Delayed-Release Tablets

Makes erosive GERD nights *good* nights™

See package insert for full Prescribing Information.

INDICATIONS AND USAGE

Maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

Short-term treatment (up to 8 weeks) of erosive esophagitis associated with GERD. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

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

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. 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.

Information for Patients

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

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.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

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 combined 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.

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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. 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

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

Use in Elderly

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

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

	% Incidence			
	Study 300-US		Study 301-US	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term double-blind or open-label clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
	Pantoprazole Total	Ranitidine 300 mg	Omeprazole 20 mg	Famotidine 40 mg
Study Event (N = 2805)	(N = 594)	(N = 474)	(N = 239)	
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more of GERD patients on long-term therapy.

Most Frequent Adverse Events Reported as Drug Related in Long-term Domestic Trials

	% Incidence	
Study Event	PROTONIX (n = 536)	Ranitidine (n = 185)
Headache	5	2
Abdominal pain	3	1
Liver function tests abnormal	2	<1
Nausea	2	2
Vomiting	2	2

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in <1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction, photosensitivity reaction.

CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

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NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

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SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In two U.S. controlled, short-term trials, 0.4 % of the patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PROTONIX 20 mg experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient tolerated a dose of 320 mg per day for 3 months. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

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.

Wyeth®

under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on the approved PROTONIX Delayed-Release Tablets direction circular (CI 7482-1, Issued June 18, 2001).

PROTONIX® tames erosive GERD night after night

In a double-blind, 12-month study

- **93%** of nights were heartburn-free[1]
- Preferred PPI for nighttime heartburn[2]*

*Based on a survey of 200 gastroenterologists who prescribed PPIs for nighttime heartburn in erosive GERD patients.

ONCE-A-DAY

PROTONIX® 40mg

(Pantoprazole Sodium) Delayed-Release Tablets

Makes erosive GERD nights *good* nights™

PROTONIX® 40mg

(Pantoprazole Sodium) Delayed-Release Tablets

Makes erosive GERD nights *good* nights™

See package insert for full prescribing information.

INDICATIONS AND USAGE

Maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD). Controlled studies did not extend beyond 12 months.

Short-term treatment (up to 8 weeks) of erosive esophagitis associated with GERD. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

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

Owing to the chronic nature of erosive esophagitis, there may be a potential for prolonged administration of pantoprazole. 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.

Information for Patients

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin, midazolam, clarithromycin, metronidazole, or amoxicillin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when coadministered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

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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.

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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.

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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. 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

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

Use in Elderly

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

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

	% Incidence			
	Study 300-US		Study 301-US	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In international short-term double-blind or open-label clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
Study Event	Pantoprazole Total (N = 2805)	Ranitidine 300 mg (N = 594)	Omeprazole 20 mg (N = 474)	Famotidine 40 mg (N = 239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

In two U.S. controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 12 months, the following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more of GERD patients on long-term therapy.

Most Frequent Adverse Events Reported as Drug Related in Long-term Domestic Trials

	% Incidence	
Study Event	PROTONIX (n = 536)	Ranitidine (n = 185)
Headache	5	2
Abdominal pain	3	1
Liver function tests abnormal	2	<1
Nausea	2	2
Vomiting	2	2

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short- and long-term domestic and international trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in pantoprazole-treated patients: anxiety, arthralgia, asthenia, back pain, bronchitis, chest pain, constipation, cough increased, dizziness, dyspepsia, dyspnea, flu syndrome, gastroenteritis, gastrointestinal disorder, hyperlipemia, hypertonia, infection, liver function tests abnormal, migraine, nausea, neck pain, pain, pharyngitis, rectal disorder, rhinitis, SGPT increased, sinusitis, upper respiratory tract infection, urinary frequency, urinary tract infection, and vomiting.

Additional treatment-emergent adverse experiences occurring in <1% of pantoprazole-treated patients from these trials are listed below by body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, nonspecified drug reaction, photosensitivity reaction.

CARDIOVASCULAR SYSTEM: abnormal electrocardiogram, angina pectoris, arrhythmia, atrial fibrillation/flutter, cardiovascular disorder, chest pain substernal, congestive heart failure, hemorrhage, hypertension, hypotension, myocardial infarction, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, neuropathy, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis; and rhabdomyolysis. In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In two U.S. controlled, short-term trials, 0.4 % of the patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PROTONIX 20 mg experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely). Significant elevations of SGOT or SGPT were defined as values at least three times the upper limit of normal that were non-sporadic and had no clear alternative explanation. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient tolerated a dose of 320 mg per day for 3 months. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

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.

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A Wyeth-Ayerst Company
Philadelphia, PA 19101
under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on the approved PROTONIX Delayed-Release Tablets direction circular (CI 7482-1, Issued June 18, 2001).

References: 1. Data on file, Wyeth-Ayerst Laboratories. **2.** *A study to determine gastroenterologists' first choice of a proton pump inhibitor for nighttime heartburn patients with erosive gastroesophageal reflux disease.* New York, NY: Guideline Research Corp; 2001:1-10.

Nighttime heartburn: a rude awakening

PROTONIX is indicated for the treatment and maintenance of healing of erosive esophagitis with associated gastroesophageal reflux disease (GERD) symptoms. Controlled studies did not extend beyond 12 months.

The most frequently reported adverse events with PROTONIX Delayed-Release Tablets are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. **Please see brief summary of Prescribing Information on last page of this advertisement.**

In two well-controlled 8-week studies, morning dosing of PROTONIX provided

Complete elimination of nighttime heartburn and regurgitation[1,2]

- In 82% of patients, symptoms disappeared and did not come back while patients were on therapy[2]

27.5 million patients treated worldwide since 1994[3]

Costs up to 28% less than other PPIs to treat erosive esophagitis[4]

ONCE-A-DAY

PROTONIX®

(Pantoprazole Sodium) 40-mg Delayed-Release Tablets

Makes erosive GERD nights *good* nights

ONCE-A-DAY

PROTONIX®

(Pantoprazole Sodium) 40-mg Delayed-Release Tablets

Makes erosive GERD nights *good* nights

See package insert for full prescribing information.

INDICATIONS AND USAGE

Short-term treatment (up to 8 weeks) of erosive esophagitis associated with gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.

The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established (see **PRECAUTIONS**).

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

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

In rodents, pantoprazole is carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these animal findings to humans is unknown. The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. PROTONIX is not indicated for maintenance therapy (see **INDICATIONS AND USAGE**).

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole has not been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed every other day in these patients.

Information for Patients

PROTONIX tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, or warfarin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

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. Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

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 combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, and 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.

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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. 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

Erosive esophagitis healing rates in the 221 women treated with pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

Use in Elderly

Erosive esophagitis healing rates in the 107 elderly patients (≥65 years old) treated with pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile, including the incidence rates of adverse events and laboratory abnormalities, in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two US controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

	% Incidence			
	Study 300-US		**Study 301-US**	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short-term domestic trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in PROTONIX-treated patients: asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain, migraine, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting, hyperlipemia, liver function tests abnormal, SGPT increased, arthralgia, anxiety, dizziness, hypertonia, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, urinary frequency, and urinary tract infection.

In international short-term double-blind or open-label, clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials

	% Incidence			
Study Event	Pantoprazole Total (N=2805)	Ranitidine 300 mg (N=594)	Omeprazole 20 mg (N=474)	Famotidine 40 mg (N=239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

Additional adverse experiences occurring in <1% of GERD patients based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, bilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole, including anaphylaxis; angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); pancreatitis; jaundice; confusion; hypokinesia; speech disorder; increased salivation; vertigo; nausea; and tinnitus.

Laboratory Values

In two US controlled trials, 0.4% of the patients on 40 mg pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

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.

References: 1. Data on file, Wyeth-Ayerst Laboratories, GMR-32023 (Protocol No. 3001A1-301-US). **2.** Data on file, Wyeth-Ayerst Laboratories, GMR-32022 (Protocol No. 3001A1-300-US). **3.** Data on file, Wyeth-Ayerst Laboratories, Pantoprazole 10th Periodic Safety Update: 24-FEB-1999 to 23-AUG-1999. **4.** *2000 Drug Topics® Red Book®: April 2000 Update.* Montvale, NJ: Medical Economics Co; 2000:19(4).

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D78467 Konstanz, Germany

This Brief Summary is based on the approved PROTONIX tablets direction circular (March 1, 2000, CI 6004-1)

Erosive GERD

can be a monster at night

Now, say goodnight to symptoms!

PROTONIX 40-mg Delayed-Release Tablets are indicated for short-term treatment (up to 8 weeks) of erosive esophagitis associated with gastroesophageal reflux disease (GERD); an additional 8-week course may be considered if necessary.

The most frequently reported adverse events with PROTONIX are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. **Please see brief summary of Prescribing Information on last page of this advertisement.**

Erosive GERD
can be a monster at night

Now for short-term treatment* of erosive esophagitis associated with GERD

Say goodnight to symptoms with New PROTONIX®

*Up to 8 weeks; an additional 8-week course may be considered if necessary.

The most frequently reported adverse events with PROTONIX are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. PROTONIX is indicated for use for up to 16 weeks. **Please see brief summary of Prescribing Information on last page of this advertisement.**

In two well-controlled 8-week studies, morning dosing of PROTONIX provided

Complete elimination of...

- Symptoms disappeared and did not come back while patients were on therapy[1,2]

Nighttime heartburn

- Twice as effective as b.i.d. nizatidine (Axid®†) on Day 1[1‡]
- In a separate study, 82% of patients had complete elimination of symptoms by Week 8[2§]

Regurgitation

- Two and a half times as effective as b.i.d. nizatidine on Day 1[1]
- In a separate study, 82% of patients had complete elimination of symptoms by Week 8[2]

† Axid is a registered trademark of Eli Lilly and Company
‡ In a double-blind study vs. nizatidine (n=237, $P<0.05$)
§ In a double-blind, placebo-controlled study (n=590, $P<0.05$)

ONCE-A-DAY

NEW PROTONIX®

(Pantoprazole Sodium) 40-mg Delayed-Release Tablets

Makes erosive GERD nights *good* nights

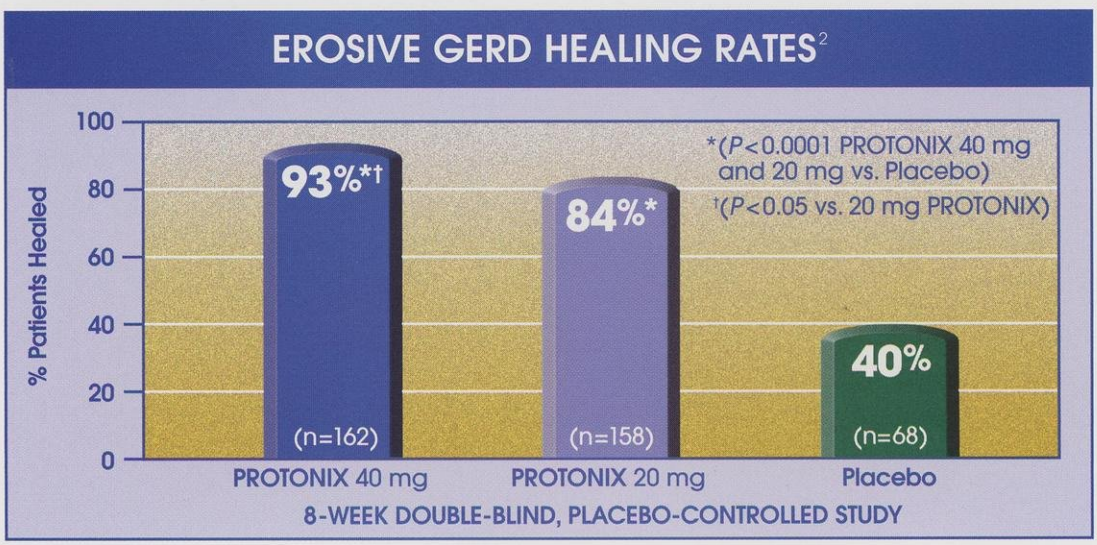
ONCE-A-DAY

NEW PROTONIX®

(Pantoprazole Sodium) 40-mg Delayed-Release Tablets

Say goodnight to erosive esophagitis (EE)

Impressive healing...nearly all patients completely healed by Week 8[2]



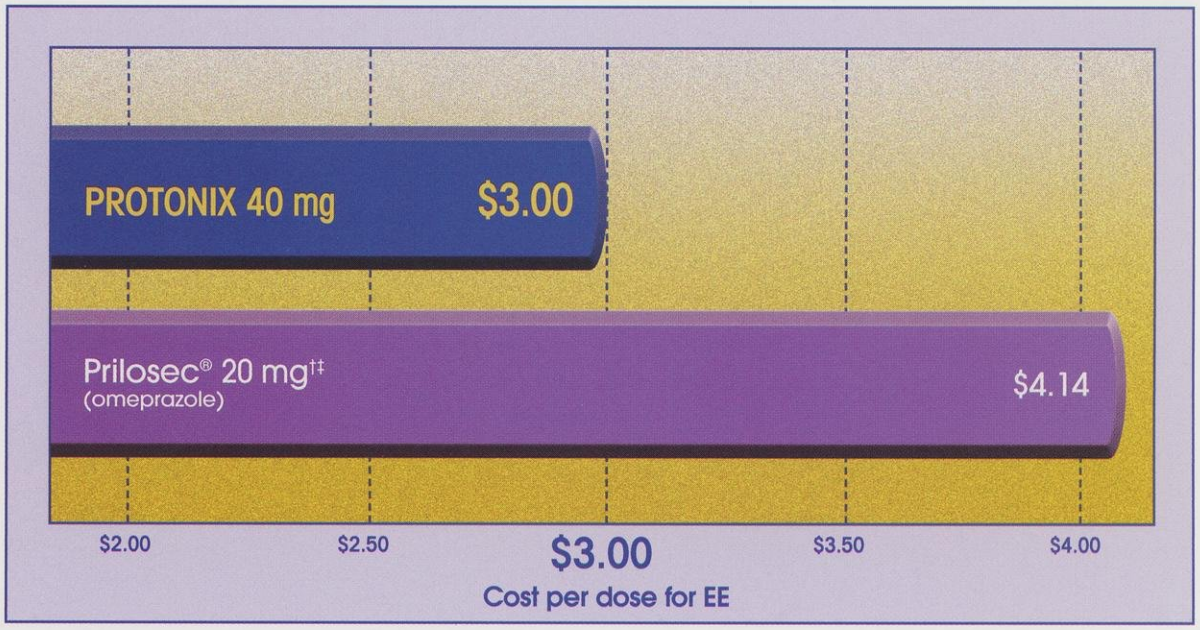
- PROTONIX 40 mg was significantly more effective than the 20-mg dose in EE healing[2]
- PROTONIX 40 mg provided superior healing rates in a separate study vs. nizatidine 150 mg b.i.d.[1]

The most frequently reported adverse events with PROTONIX are headache and diarrhea. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX is contraindicated in patients with known hypersensitivity to any component of the formulation. PROTONIX is indicated for use for up to 16 weeks. **Please see brief summary of Prescribing Information on last page of this advertisement.**

27.5 million patients treated worldwide since 1994[3]

- Clinical experience in over 60 countries[4]
- Documented in 100 clinical studies involving more than 45,000 patients worldwide[3,5]
- No known clinically relevant drug interactions

Costs up to 28% less than Prilosec to treat erosive esophagitis*



* Short-term treatment (up to 8 weeks); an additional 8-week course may be considered if necessary.

† Based on average wholesale prices (AWPs) in *2000 Drug Topics® Red Book®: April 2000 Update.*[6] AWP is suggested by Wyeth-Ayerst Laboratories to certain independent pricing services, which publish AWPs for generic pharmaceutical products. Wyeth-Ayerst makes no representation that AWP represents an actual price charged for its products.

‡ Prilosec is a registered trademark of Astra AB.

ONCE-A-DAY

NEW PROTONIX®

(Pantoprazole Sodium) 40-mg Delayed-Release Tablets

Makes erosive GERD nights *good* nights

See package insert for full prescribing information.

INDICATIONS AND USAGE

Short-term treatment (up to 8 weeks) of erosive esophagitis associated with gastroesophageal reflux disease (GERD). For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered.

The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established (see **PRECAUTIONS**).

CONTRAINDICATIONS

Known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

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

In rodents, pantoprazole is carcinogenic and caused rare types of gastrointestinal tumors. The relevance of these animal findings to humans is unknown. The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. PROTONIX is not indicated for maintenance therapy (see **INDICATIONS AND USAGE**).

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole has not been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed every other day in these patients.

Information for Patients

PROTONIX tablets should be swallowed whole, with or without food in the stomach and should not be split, crushed, or chewed. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, or warfarin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

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.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

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 combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, and 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.

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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. 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

Erosive esophagitis healing rates in the 221 women treated with pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

Use in Elderly

Erosive esophagitis healing rates in the 107 elderly patients (≥65 years old) treated with pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile, including the incidence rates of adverse events and laboratory abnormalities, in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two US controlled clinical trials involving PROTONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably, or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PROTONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials
% Incidence

	Study 300-US		Study 301-US	
Study Event	PROTONIX (n = 521)	Placebo (n = 82)	PROTONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eructation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short-term domestic trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥1% in PROTONIX-treated patients: asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain, migraine, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting, hyperlipemia, liver function tests abnormal, SGPT increased, arthralgia, anxiety, dizziness, hypertonia, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, urinary frequency, and urinary tract infection.

In international short-term double-blind or open-label, clinical trials involving 20 to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Adverse Events in GERD Patients in Short-term International Trials
% Incidence

Study Event	Pantoprazole Total (N=2805)	Ranitidine 300 mg (N=594)	Omeprazole 20 mg (N=474)	Famotidine 40 mg (N=239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

Additional adverse experiences occurring in <1% of GERD patients based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, bilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the postmarketing use of pantoprazole, including anaphylaxis; angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); pancreatitis; jaundice; confusion; hypokinesia; speech disorder; increased salivation; vertigo; nausea; and tinnitus.

Laboratory Values

In two US controlled trials, 0.4% of the patients on 40 mg pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

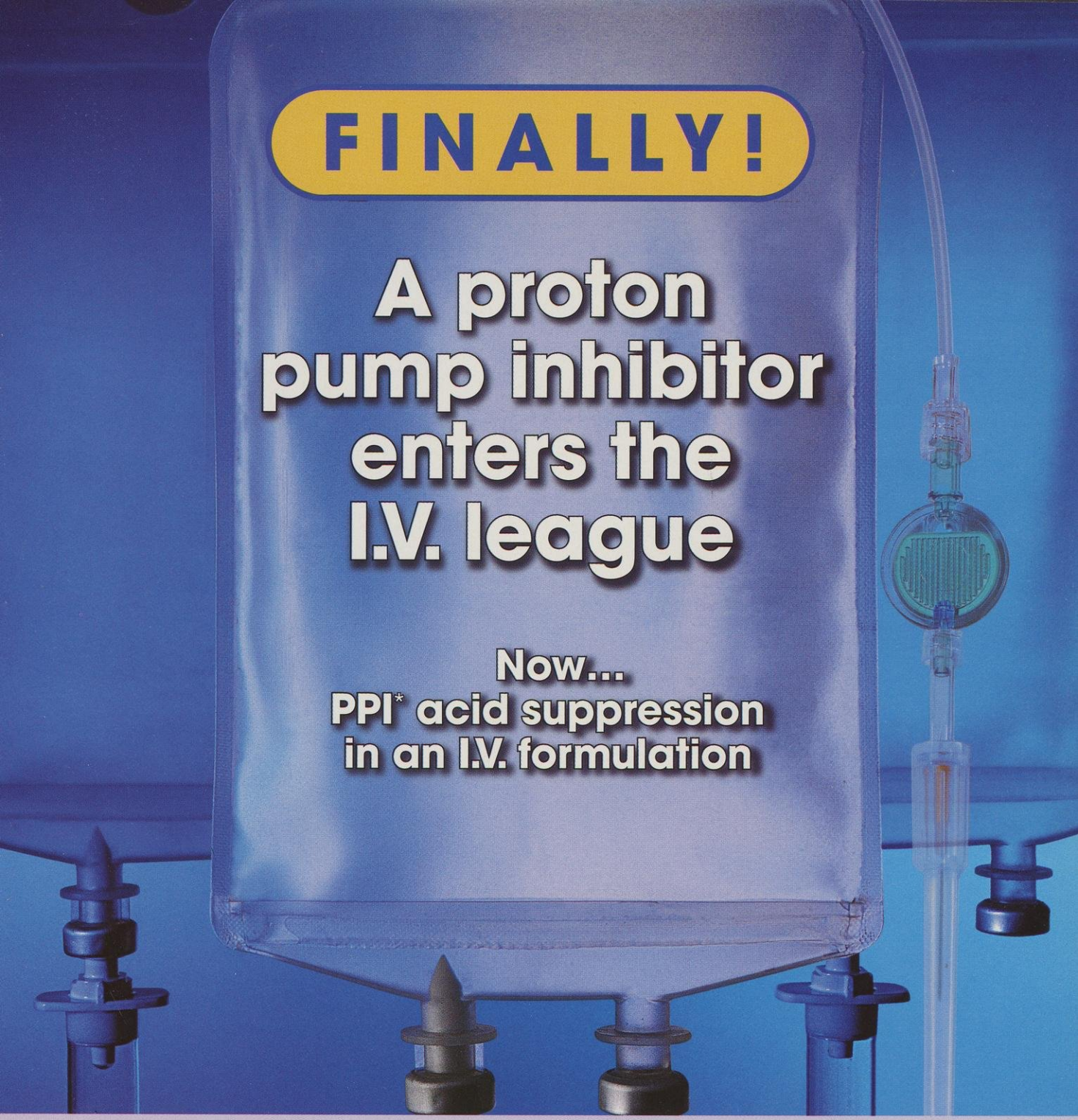
Pantoprazole is not removed by hemodialysis.

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.

Manufactured for Wyeth Laboratories
A Wyeth-Ayerst Company
Philadelphia, PA 19101
under license from
Byk Gulden Pharmaceuticals
D78467 Konstanz, Germany

This Brief Summary is based on the approved PROTONIX tablets direction circular (March 1, 2000, CI 6004-1)

References: 1. Data on file, Wyeth-Ayerst Laboratories, GMR-32023 (Protocol No. 3001A1-301-US). **2.** Data on file, Wyeth-Ayerst Laboratories, GMR-32022 (Protocol No. 3001A1-300-US). **3.** Data on file, Wyeth-Ayerst Laboratories, Pantoprazole 10th Periodic Safety Update: 24-FEB-1999 to 23-AUG-1999. **4.** Data on file, Wyeth-Ayerst Laboratories, Commercial Marketing Summary for Protonix. **5.** Data on file, Wyeth-Ayerst Laboratories, Table of Studies for Pantoprazole Tablets. **6.** *2000 Drug Topics® Red Book®: April 2000 Update.* Montvale, NJ: Medical Economics Co; 2000:19(4).



PROTONIX I.V. is indicated for short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), **as an alternative to oral therapy in patients who are unable to continue taking PROTONIX Delayed-Release Tablets.** Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated.

The most frequently reported adverse events with PROTONIX I.V. are abdominal pain, chest pain, rash, and pruritus. Symptomatic response to therapy does not preclude the presence of gastric malignancy. PROTONIX I.V. is contraindicated in patients with known hypersensitivity to any component of the formulation. Treatment with PROTONIX I.V. should be discontinued as soon as the patient is able to be treated with PROTONIX Delayed-Release Tablets.

NEW

PROTONIX® I.V.

(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

Please see brief summary of Prescribing Information on reverse side of this advertisement.

NEW PROTONIX® I.V.

(Pantoprazole Sodium) For Injection

The first and only I.V. PPI

See package insert for full prescribing information.

INDICATIONS AND USAGE

Short-term treatment (7 to 10 days) of gastroesophageal reflux disease (GERD), **as an alternative in patients who are unable to continue taking PROTONIX (pantoprazole sodium) Delayed-Release Tablets.** Safety and efficacy of PROTONIX I.V. for Injection as an initial treatment for GERD have not been demonstrated.

CONTRAINDICATIONS

Patients with known hypersensitivity to the formulation.

PRECAUTIONS

General

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

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole have not yet been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (<21%), when dosed as recommended at 40 mg once daily, needs to be weighed against the potential for reduced acid control when decreasing the dose or altering the dosing regimen in these patients.

Treatment with PROTONIX I.V. for Injection should be discontinued as soon as the patient is able to resume treatment with PROTONIX Delayed-Release Tablets.

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 (a CYP3A4 substrate), metoprolol (a CYP2D6 substrate), diclofenac (a CYP2C9 substrate) and theophylline (a CYP1A2 substrate) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *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 and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2D6, 2C9, and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

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 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.

Sporadic occurrences of hepatocellular adenomas and a hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month oral toxicity studies.

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 combined hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

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.

Pantoprazole 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) was found to have no effect on fertility and reproductive performance.

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology 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.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. 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.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

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

Use in Elderly

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 GERD. Erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with oral pantoprazole in US 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. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of oral pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS

Safety Experience with Intravenous Pantoprazole

Intravenous pantoprazole has been well tolerated in clinical trials of GERD patients and healthy subjects. A double-blind placebo controlled study in the U.S. evaluated the effect of PROTONIX I.V. for Injection on pentagastrin-stimulated acid secretion in 65 GERD patients. Treatment-emergent events considered possibly, probably or definitely drug-related that were reported by 2 or more patients (≥ 4%) taking PROTONIX I.V. (pantoprazole sodium) for Injection (n=50) and by 0% of patients taking placebo (n=15) were: abdominal pain (12%), chest pain (6%), rash (6%), and pruritus (4%). Additional adverse experiences occurring in >1% of GERD patients treated with intravenous pantoprazole (n=412) in domestic (n=50) or international (n=362) clinical trials are shown below by body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS A WHOLE: headache, injection site reaction.

DIGESTIVE SYSTEM: dyspepsia, nausea, diarrhea, vomiting.

NERVOUS SYSTEM: dizziness.

RESPIRATORY SYSTEM: rhinitis.

The safety of intravenous pantoprazole has also been evaluated during international clinical trials conducted in over 300 critically ill patients. The safety profile of intravenous pantoprazole was similar to that of oral pantoprazole with the exception of injection site reactions including injection site inflammation, thrombophlebitis, hemorrhage, and abscess. Head-to-head comparative studies between PROTONIX I.V. for Injection and oral PROTONIX, other proton pump inhibitors (oral or I.V.) or H2 receptor antagonists (oral or I.V.) have been limited. The available information does not provide sufficient evidence to distinguish the safety profile of these regimens.

Safety Experience with Oral Pantoprazole

In short-term clinical trials in GERD patients treated with oral pantoprazole, the following adverse events, regardless of causality, occurred at a rate of ≥ 1%.

BODY AS A WHOLE: headache, asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain.

CARDIOVASCULAR SYSTEM: migraine.

DIGESTIVE SYSTEM: diarrhea, flatulence, abdominal pain, eructation, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting.

HEPATO-BILIARY SYSTEM: liver function tests abnormal, SGPT increased.

METABOLIC AND NUTRITIONAL: hyperglycemia, hyperlipidemia.

MUSCULOSKELETAL SYSTEM: arthralgia.

NERVOUS SYSTEM: insomnia, anxiety, dizziness, hypertonia.

RESPIRATORY SYSTEM: bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection.

SKIN AND APPENDAGES: rash.

UROGENITAL SYSTEM: urinary frequency, and urinary tract infection.

Additional adverse experiences occurring in <1% of GERD patients receiving oral pantoprazole based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances, the relationship to pantoprazole was unclear.

BODY AS WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, hyperbilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthrosis, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating; urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with postmarketing use of intravenous or oral pantoprazole, including anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); pancreatitis; jaundice; confusion; hypokinesia; speech disorder; increased salivation; vertigo; nausea; and tinnitus.

In addition, also observed have been confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, tinnitus, and blurred vision.

Laboratory Values

In U.S. and international GERD clinical trials, the overall percentages of transaminase elevations did not increase during treatment with intravenous pantoprazole. For other laboratory parameters, there were no clinically important changes identified.

In two U.S. controlled trials of oral pantoprazole in patients with GERD, 0.4% of the patients on 40 mg oral pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of oral pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

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.

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