**EXHIBIT-III**

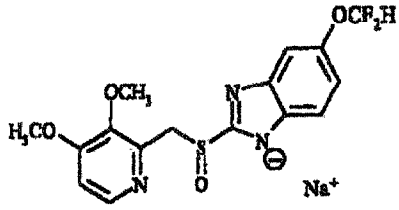
# PROTONIX® I.V.

(pantoprazole sodium)
**for Injection**

] only

## DESCRIPTION

The active ingredient in PROTONIX® I.V. (pantoprazole sodium) for Injection is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl] sulfinyl]-1H-benzimidazole, a compound that inhibits gastric acid secretion. Its empirical formula is $C_{16}H_{14}F_2N_3NaO_4S$, with a molecular weight of 405.4. The structural formula is:




Pantoprazole sodium is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane. The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. The reconstituted solution of PROTONIX I.V. for Injection is in the pH range 9.0 to 10.5.

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

## CLINICAL PHARMACOLOGY

### Pharmacokinetics

Pantoprazole peak serum concentration ($C_{max}$) and area under the serum concentration-time curve (AUC) increase in a manner proportional to intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing. Following the administration of PROTONIX I.V. for Injection, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see CLINICAL PHARMACOLOGY, Metabolism) with normal liver function receiving a 40 mg dose of PROTONIX I.V. for Injection by constant rate over 15 minutes, the peak concentration ($C_{max}$) is 5.52 μg/mL and the total area under the plasma concentration versus time curve (AUC) is 5.4 μg · hr/mL. The total clearance is 7.6-14.0 L/h and the apparent volume of distribution is 11.0-23.6 L.

### *Distribution*

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

### *Metabolism*

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

### *Elimination*

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

### *Special Populations*

#### *Geriatric*

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

#### *Pediatric*

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

#### *Gender*

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

#### *Renal Impairment*

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

#### *Hepatic Impairment*

Oral administration studies (absolute bioavailability is approximately 70%) were performed in patients with mild to severe hepatic impairment. Maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum elimination half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration equal to or less than 21%. No dosage adjustment is needed in patients with mild to severe hepatic impairment. Doses higher than 40 mg/day have not been studied in hepatically-impaired patients.

## Drug-Drug Interactions

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

## Pharmacodynamics

### *Mechanism of Action*

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

### *Antisecretory Activity*

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

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

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

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

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

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

### *Serum Gastrin Effects*

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

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

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

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

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

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

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

### *Other Effects*

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given orally once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyronine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

## Clinical Studies

### Gastroesophageal Reflux Disease (GERD) Associated With a History of Erosive Esophagitis

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

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

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

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

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

To evaluate the effectiveness of PROTONIX I.V. (pantoprazole sodium) for Injection as an initial treatment to suppress gastric acid secretion, two studies were conducted.

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

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

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

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

Study 2 was a single-center, double-blind, parallel-group study to compare the clinical effects of PROTONIX I.V. for Injection and oral PROTONIX. Patients (n=45, median age 56 years, 21 males and 24 females) with acute endoscopically proven reflux esophagitis (Savary/Miller Stage II or III) with at least 1 of 3 symptoms typical for reflux esophagitis (acid eructation, heartburn, or pain on swallowing) were randomized to receive either 40 mg intravenous pantoprazole or 40 mg oral pantoprazole daily for 5 days. After the initial 5 days, all patients were treated with 40 mg oral pantoprazole daily to complete a total of 8 weeks of treatment. Symptom relief was assessed by calculating the daily mean of the sums of the average scores for these 3 symptoms and the daily mean of the average score for each of the symptoms separately. There was no significant difference in symptom relief between PROTONIX I.V. and oral PROTONIX therapy within the first 5 days. A repeat endoscopy after 8 weeks of treatment revealed that 20 out of 23 (87%) of the PROTONIX I.V. plus oral PROTONIX patients and 19 out of 22 (86%) of the oral PROTONIX patients had endoscopically proven healing of their esophageal lesions.

Data comparing PROTONIX I.V. for Injection to other proton pump inhibitors (oral or I.V.) or H2 receptor antagonists (oral or I.V.) are limited, and therefore, are inadequate to support any conclusions regarding comparative efficacy.

### Pathological Hypersecretion Associated with Zollinger-Ellison Syndrome

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

In the other study of 14 patients (38 to 67 years; 5 female; 2 black, 12 white) with Zollinger-Ellison Syndrome, treatment was switched from an oral proton pump inhibitor to PROTONIX I.V. for Injection. PROTONIX I.V. for Injection maintained or improved control of gastric acid secretion.

In both studies, PROTONIX I.V. for Injection 160 or 240 mg per day in divided doses maintained basal acid secretion below target levels in all patients. Target levels were 10 mEq/h in patients without prior gastric surgery, and 5 mEq/h in all patients with prior gastric acid-reducing surgery. Once gastric acid secretion was controlled, there was no evidence of tolerance during this 7 day study. Basal acid secretion was maintained below target levels for at least 24 hours in all patients and through the end of treatment in these studies (3 to 7 days) in all but 1 patient who required a dose adjustment guided by acid output measurements until acid control was achieved. In both studies, doses were adjusted to the individual patient need, but gastric acid secretion was controlled in greater than 80% of patients by a starting regimen of 80 mg q12h.

## INDICATIONS AND USAGE

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

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

### Pathological Hypersecretion Associated with Zollinger-Ellison Syndrome

PROTONIX I.V. for Injection is indicated for the treatment of pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions.

## CONTRAINDICATIONS

PROTONIX I.V. for Injection is contraindicated in patients with known hypersensitivity to 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.

As with any other intravenous product containing edetate disodium (the salt form of EDTA) which is a potent chelator of metal ions including zinc, zinc supplementation should be considered in patients treated with PROTONIX I.V. for Injection who are prone to zinc deficiency. Caution should be used when other EDTA containing products are also co-administered intravenously.

Treatment with PROTONIX® I.V. (pantoprazole sodium) 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 through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. (See **CLINICAL PHARMACOLOGY**, **Drug-Drug Interactions**.)

Based on studies evaluating possible interactions of pantoprazole with other drugs, no dosage adjustment is needed with concomitant use of the following: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam (and its active metabolite, desmethyldiazepam), diclofenac, naproxen, piroxicam, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, warfarin (see below), midazolam, clarithromycin, metronidazole, or amoxicillin. 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. There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including pantoprazole, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

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

## 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 most proton pump inhibitors, including pantoprazole. An alternative confirmatory method should be considered to verify positive results.

## ADVERSE REACTIONS

### Safety Experience with Intravenous Pantoprazole

Intravenous pantoprazole has been studied in clinical trials in several populations including patients with GERD and a history of erosive esophagitis, patients with Zollinger-Ellison Syndrome, patients involved in clinical trials for other disorders which may respond to proton pump inhibitor therapy, and healthy subjects. Adverse experiences occurring in >1% of patients treated with intravenous pantoprazole (n=836) in domestic or 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, dizziness.

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, hyperlipemia.

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 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, non-specified 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 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; elevated CPK (creatine phosphokinase); severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; interstitial nephritis; 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 with GERD and 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 may be administered intravenously through a dedicated line or through a Y-site. The intravenous line should be flushed before and after administration of PROTONIX I.V. for Injection with either 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP. When administered through a Y-site, PROTONIX I.V. for Injection is compatible with the following solutions: 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP.

Midazolam HCl has been shown to be incompatible with Y-site administration of PROTONIX I.V. for Injection. PROTONIX I.V. for Injection may not be compatible with products containing zinc. When PROTONIX I.V. for Injection is administered through a Y-site, immediately stop use if precipitation or discoloration occurs.

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

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 the 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. Doses higher than 40 mg/day have not been studied in hepatically-impaired 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 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 with GERD and a history of erosive esophagitis for more than 10 days have not been demonstrated (see **INDICATIONS AND USAGE**).

*Fifteen Minute Infusion*

PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, and further diluted (admixed) with 100 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a final concentration of approximately 0.4 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 22 hours at room temperature prior to intravenous infusion. Both the reconstituted solution and the admixed solution do not need to be protected from light.

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

*Two Minute Infusion*
PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, to a final concentration of approximately 4 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to intravenous infusion and does not need to be protected from light. PROTONIX I.V. for Injection should be administered intravenously over a period of at least 2 minutes.

### 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.) 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.

*Fifteen Minute Infusion*
Each vial of PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP. The contents of the two vials should be combined and further diluted (admixed) with 80 mL of 5% Dextrose Injection, USP, 0.9% Sodium Chloride Injection, USP, or Lactated Ringer's Injection, USP, to a total volume of 100 mL with a final concentration of approximately 0.8 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to further dilution; the admixed solution may be stored for up to 22 hours at room temperature prior to intravenous infusion. Both the reconstituted solution and the admixed solution do not need to be protected from light.

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

*Two Minute Infusion*
PROTONIX I.V. for Injection should be reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP, per vial to a final concentration of approximately 4 mg/mL. The reconstituted solution may be stored for up to 2 hours at room temperature prior to intravenous infusion and does not need to be protected from light. The total volume from both vials should be administered intravenously over a period of at least 2 minutes.

## HOW SUPPLIED

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

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

NDC 0008-0923-51 One carton containing 1 vial of PROTONIX I.V. for Injection (each vial containing 40-mg pantoprazole).

**Storage**

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

Caution: the reconstituted product should not be frozen.

U.S. Patent No. 4,758,579

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D78467 Konstanz, Germany

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