

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
22-020

PHARMACOLOGY REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER:	22-020
SERIAL NUMBER:	000
DATE RECEIVED BY CENTER:	5/15/2006
PRODUCT:	Protonix (pantoprazole sodium, 40 mg) Delayed Release 
INTENDED CLINICAL POPULATION:	Short term treatment of patients with gastroesophageal reflux disease (GERD) and history of erosive esophagitis, maintenance of healing erosive esophagitis and pathological hypersecretory conditions including Zollinger-Ellis Syndrome.
SPONSOR:	Wyeth Pharmaceuticals, Philadelphia, PA.
DOCUMENTS REVIEWED:	Electronic submission of the NDA
REVIEW DIVISION:	Division of Gastroenterology Products (HFD-180)
PHARM/TOX REVIEWER:	Sushanta Chakder, Ph.D.
PHARM/TOX SUPERVISOR:	Jasti B. Choudary, B.V.Sc., Ph.D.
DIVISION DIRECTOR:	Brian Harvey, M. D., Ph. D.
PROJECT MANAGER:	Thomas Moreno

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Date of review submission to Division File System (DFS): March 09, 2007

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Executive Summary

I. Recommendations

- A. **Recommendation on Approvability:** From a preclinical standpoint, the NDA application is approvable.
- B. **Recommendation for Nonclinical Studies:** None.
- C. **Recommendations on Labeling:** No changes in the preclinical section of the current labeling are recommended.

II. Summary of Nonclinical Findings

A. Brief overview of nonclinical findings:

Pantoprazole delayed release tablets (Protonix tablets) are currently marketed in the U.S. for use in maintenance of healing of erosive esophagitis, for the control of heartburn symptoms in patients with gastroesophageal reflux disease (GERD) and for use in pathological hypersecretory conditions including Zollinger-Ellison syndrome. The sponsor submitted NDA 22-020 for an enteric-coated pantoprazole sodium granules formulation for the same indications. The sponsor conducted a pharmacokinetic study in which the relative bioavailabilities of pantoprazole sodium and pantoprazole magnesium spheroids formulations were compared with those of the marketed delayed release tablet product and an uncoated tablet preparation in male beagle dogs following a single oral dosing. No other preclinical studies were provided, and the sponsor referred to NDA 20-987 (Protonix Delayed Release Tablets) under which the preclinical profiles of pantoprazole sodium have been well-characterized.

The nonclinical pharmacology studies show that pantoprazole is a potent and long-lasting inhibitor of gastric acid secretion. The binding of pantoprazole to H^+/K^+ -ATPase is irreversible in nature, and effectively inhibits acid secretion until new enzyme is synthesized. In vivo studies with pantoprazole administered by the oral or intravenous route to rats demonstrated inhibition of basal acid secretion as well as secretion induced by 2-deoxy-D-glucose, bethanecol and pentagastrin. Oral pantoprazole inhibited or abolished aspirin-, stress- or acidified ethanol- induced gastric mucosal lesions in rats as well as gastric and duodenal ulcers induced by acetic acid. Inhibition of gastric mucosal lesions paralleled inhibition of gastric acid secretion.

Following oral administration pantoprazole to mice, rats, dogs and monkeys, plasma C_{max} and AUC values for total radioactivity/and or the parent drug increased with increasing dose, although, generally not in a dose-proportional manner. The C_{max} and AUC values for unchanged drug in rats, mice, dogs and monkeys encompassed values in healthy human volunteers receiving a 40 mg (0.8 mg/kg) dose. The bioavailability of pantoprazole following an oral dose of 5 mg/kg in rats and a 60 mg/kg in dogs were 31% and 44%, respectively. The half-lives of the parent compound in most species were generally < 1.0 hr. The bioavailability

of an oral therapeutic dose of 40 mg in healthy volunteers ranged from 47.3% to 90.8%. Pantoprazole binding to rat and human serum protein exceeded 95%. In pregnant rats, pantoprazole-related radioactivity crossed the placental barrier, and in lactating rats, the radioactivity was secreted in milk. In human liver microsomes, pantoprazole was mainly metabolized by CYP2C19 and CYP3A4. Pantoprazole acted as a specific inducer of CYP2B1 and CYP2B2 isozymes.

Following oral administration of single doses to male dogs, the pantoprazole sodium encapsulated enteric-coated spheroids exhibited a mean plasma exposure (dose normalized) similar from that of the marketed tablet product; however, the C_{max} for the spheroid formulation was lower than that of the marketed tablet product.

The toxicity of pantoprazole was evaluated in acute oral and intravenous studies in mice, rats and dogs, in repeat dose oral studies in rats and dogs, and in repeat dose i.v. studies in rats, dogs and monkeys for up to 1 month. In acute toxicity studies in mice, the maximum non-lethal doses were 750 and 500 mg/kg in males and females, respectively, and in rats, the oral minimal lethal dose was 900 mg/kg for both males and females. In beagle dogs, following oral administration, the maximal non-lethal and minimum lethal doses were 300 and 1000 mg/kg, respectively. Clinical signs observed in mice, rats and dogs following oral or intravenous pantoprazole included decreased activity and ataxia. Following repeated oral administration in rats, treatment-related increases in the gastrin levels, along with increased incidences of chief cell and parietal cell hyperplasia were observed. Increased incidences of parietal cell degeneration/vacuolation were also observed in rats receiving pantoprazole for 4 weeks to 6 months. In addition, enterochromaffin-like (ECL) cell hyperplasia was observed in animals receiving the drug for one year. The effects of pantoprazole in the stomach may be related to its pharmacological actions secondary to elevated gastrin levels. Centrilobular swelling of the hepatocytes and hepatocellular hypertrophy were observed in animals receiving pantoprazole. In addition, hepatocellular necrosis was observed in rats treated with ≥ 50 mg/kg pantoprazole for 12 months. Pantoprazole-induced hepatocellular hypertrophy may be related to its drug metabolizing enzyme inducing effects. Changes in the thyroid gland (change in cellular morphology, proliferation of c-cells, follicular hypertrophy) were also observed in rats receiving the drug. In dogs, one of the target organs of toxicity was also the stomach, and the changes in the stomach included parietal cell vacuolation, increased height of the fundic mucosa, increased fundic mucosal folding, dilation of fundic glands, cellular debris in the lumen of dilated glands and increased chromogranin-positive cells in the fundic region. In addition to stomach, dilated crypts were observed in the duodenum, cecum, colon and rectum of dogs receiving pantoprazole for 6 months. Hypertrophy of the thyroid follicular cells was also observed in dogs receiving pantoprazole. Pulmonary edema along with alveolar foamy macrophages and effusion of proteinaceous fluid in the alveoli were observed in dogs receiving pantoprazole. The lung injury in dogs appeared to be most severe 3-5 days after initiation of treatment, with resolution of changes occurring with continued treatment. A thiourea-like metabolite of pantoprazole (C 97165) is thought to be responsible for the induction of pulmonary edema in dogs.

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The genotoxic potential of pantoprazole was evaluated in a battery of *in vitro* and *in vivo* genotoxicity assays. *In vitro* studies included the bacterial reverse mutation assay, human lymphocyte chromosomal aberration assay, Chinese hamster ovary cell hypoxanthine guanine

phosphoribosyl transferase (CHO/HGRPT) forward mutation assay, unscheduled DNA synthesis assay with rat hepatocytes, AS52/GPT mammalian cell-forward gene mutation assay, thymidine kinase mutation test with mouse lymphoma L5178Y cells, and malignant transformation assay with C3H M2 fibroblasts. *In vivo* studies included the mouse micronucleus assay, the rat bone marrow chromosomal aberration assay, measurement of DNA binding in rats, and ³²P-postlabeling experiment with liver DNA. Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two 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* bacterial reverse mutation assay (Ames assay), the 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.

The carcinogenic potential of pantoprazole was evaluated in 24-month oral studies in mice (B6C3F1) and two strains of rats (Sprague-Dawley and Fischer 344), and in a 26-week oral study in p53^{+/-} heterozygous mice. Pantoprazole was carcinogenic in both rats and mice. In a 24-month carcinogenicity study in Sprague-Dawley rats, groups of animals were treated orally with pantoprazole doses of 0.5 to 200 mg/kg/day. In the gastric fundus, treatment of 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment with 50 and 200 mg/kg/day doses of pantoprazole 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 rats were treated orally with doses of 5 to 50 mg/kg/day. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) hyperplasia and benign and malignant neuroendocrine cell tumors. However, dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with pantoprazole doses of 5 to 150 mg/kg/day. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

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

Pantoprazole was evaluated in fertility and general reproductive performance studies in rats, developmental toxicity studies in rats and rabbits, and peri- and post- natal development

studies in rats. Pantoprazole at oral doses up to 500 mg/kg/day in male rats and 450 mg/kg/day in female rats was found to have no effects on fertility and general reproductive performance. Segment II teratology studies have been conducted in pregnant Sprague Dawley rats at oral doses up to 450 mg/kg/day, and in pregnant rabbits at oral doses up to 40 mg/kg/day. Pantoprazole did not show any evidence of teratogenicity in these studies. However, a dose-dependent delay of ossification for fetal cranial bones was observed for dams receiving 15 mg/kg/day and higher doses.

In an oral Segment III peri- and post- natal development study in Sprague Dawley rats, pantoprazole at oral doses up to 30 mg/kg/day had no significant effect on perinatal and postnatal development. However, the body weight gain of pups at 30 mg/kg/day was significantly reduced (19-22%) during the lactation period as compared with the control values.

B. Pharmacologic Activity:

Pantoprazole suppresses gastric acid secretion by specific inhibition of the enzyme, H^+ , K^+ -ATPase at the surface of the gastric parietal cells. Nonclinical pharmacology studies show that pantoprazole is a potent and long-lasting inhibitor of gastric acid secretion. The binding of pantoprazole to H^+/K^+ -ATPase is irreversible in nature, and effectively inhibits acid secretion until new enzyme is synthesized. In vivo studies with pantoprazole administered by the oral or intravenous route to rats demonstrated inhibition of basal acid secretion as well as secretion induced by 2-deoxy-d-glucose, bethanecol and pentagastrin.

C. Nonclinical Safety Issues Relevant to Clinical Use: The following nonclinical safety issues are relevant to the clinical use of the drug: the genotoxic activity of pantoprazole in both *in vitro* and *in vivo* assays, and the tumorigenicity in rats and mice.

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PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 22-020

Review number: 01

Sequence number/date/type of submission: 000/Original/May 12, 2006

Information to sponsor: Yes () No (X)

Sponsor and/or agent: Wyeth Pharmaceuticals, Philadelphia, PA.

Manufacturer for drug substance: Altana Pharma, Konstanz, Germany.

Reviewer name: Sushanta Chakder, Ph.D.

Division name: Division of Gastroenterology Products

HFD #: 180

Review completion date: 3/9/07

Drug:

Trade name: Protonix Delayed Release

Generic name: Pantoprazole sodium

Code name: N/A

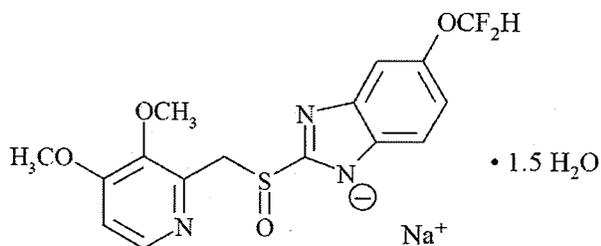
Chemical name: Sodium 5-(difluoromethoxy)-2-[[[(3-dimethoxy-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole sequehydrate.

CAS registry number: 73590-58-6

Molecular formula/molecular weight: C₁₆H₁₄F₂NaO₄S x 1.5 H₂O/432.4

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Structure:



Relevant INDs/NDAs/DMFs:

IND 68, 011, Pantoprazole sodium delayed release spheroids, Wyeth Pharmaceuticals, Philadelphia, PA.

NDA 20-987, Pantoprazole sodium (Protonix 40 mg) Tablets, Wyeth Pharmaceuticals, Philadelphia, PA.

Drug class: Gastric parietal cell H⁺, K⁺-ATPase (Proton pump) inhibitor.

Intended clinical population: Pantoprazole sodium is indicated for short term treatment of patients with gastroesophageal reflux disease (GERD) and history of erosive esophagitis, maintenance of healing erosive esophagitis and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

Clinical formulation: Each unit dose of Protonix granules contains 40 mg pantoprazole sodium, and the following excipients:

<u>Excipient</u>		<u>Compendial Status</u>
Microcrystalline Cellulose		Ph. Eur./NF
Croscopovidone		Ph. Eur./NF
Hypromellose C	U	Ph. Eur./USP
Sodium Carbonate C	U	Ph. Eur./NF
Polysorbate 80		Ph. Eur./NF
C	U	Ph. Eur./USP
Povidone C	U	Ph. Eur./USP
Hypromellose C	U	Ph. Eur./USP
Ferric Oxide, Yellow C	U	NF
Titanium Dioxide		Ph. Eur./USP
Methacrylic Acid Copolymer C	U	Ph. Eur./NF
Triethyl Citrate		Ph. Eur./NF
Hypromellose C	U	Ph. Eur./USP
Talc (Talcum)		Ph. Eur./USP

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Route of administration: Oral

Studies reviewed within this submission: The sponsor submitted the study report of a pharmacokinetic study in dogs to determine the bioavailability of pantoprazole from prototype formulations for oral delivery. The study report was reviewed.

2.6.2 PHARMACOLOGY

No Pharmacology study reports were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

N/A

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

Study title: Bioavailability of Pantoprazole in Beagle Dogs: Evaluation of Prototype Formulations for Oral Delivery (Reference # 2003-0240, 7631 RPT-50757).

Methods: The relative bioavailability of pantoprazole was assessed in male beagle dogs following oral administration of encapsulated enteric-coated spheroids formulations of pantoprazole sodium or pantoprazole magnesium. Pantoprazole sodium marketed tablet and

pantoprazole sodium uncoated tablet were administered to dogs as reference standards. Single doses of each of the four formulations were administered to fasted dogs (n = 6; mean body weight, 9.7 kg) in a four-period, non-randomized crossover study. The marketed tablet product (Batch # A98D015) was administered at 20 mg/kg, and all other formulations were administered at 40 mg/kg. The uncoated tablet was administered to animals that were pre- and post- dose-treated with a solution (15 ml) of sodium hydrogen carbonate (1.4%). All other formulations were administered with 10 ml tap water. The dosing protocol is summarized below.

In period 1, all six dogs received one 20 mg pantoprazole sodium tablet (marketed product).

In period 2, dogs 1-3 received one 40 mg pantoprazole magnesium encapsulated enteric-coated spheroids, and dogs 4-6 received one 40 mg pantoprazole sodium uncoated tablet.

In period 3, dogs 1-3 received one 40 mg pantoprazole sodium uncoated tablet, and dogs 4-6 received one 40 mg pantoprazole magnesium encapsulated enteric coated spheroids.

In period 4, all six dogs received one 40 mg pantoprazole sodium encapsulated enteric coated spheroids.

Blood samples were collected from the jugular vein at 0 (pre-dose), 0.25, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 8 and 24 hours after dosing. Plasma pantoprazole levels were determined by a reverse-phase HPLC method with UV detection. Non-compartmental pharmacokinetic analyses were performed on the dog plasma pantoprazole concentration-time profiles. Pharmacokinetic data from the marketed product (administered at 20 mg) was dose-normalized to 40 mg to allow comparison to the other three formulations.

Results: The two reference formulations, marketed tablet product and uncoated tablet provided similar exposures, with mean $AUC_{0-\alpha}$ values of 14578 and 17742 ng.hr/ml and mean C_{max} values of 10570 and 11259 ng/ml, respectively. The pantoprazole sodium encapsulated enteric-coated spheroids provided similar total exposure (mean $AUC_{0-\alpha}$ ratio, 106%) to the marketed tablet product. However, the peak plasma concentration (C_{max}) of the spheroid formulation was lower than that of the marketed tablet product (mean C_{max} ratio, 59%). Pantoprazole sodium encapsulated spheroids had shorter lag time than that of the marketed tablet product (0.25 versus 1.42 hr, respectively), and exhibited less variability in the mean plasma levels. Pantoprazole magnesium encapsulated spheroids had lower bioavailability than the marketed tablet product, and both the $AUC_{0-\alpha}$ and C_{max} ratios were lower than that for the marketed product ($AUC_{0-\alpha}$ ratio, 70%; C_{max} ratio, 32%). The pharmacokinetic parameters for the four formulations are summarized in the Table below.

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TABLE 9. MEAN (SD) PHARMACOKINETIC PARAMETERS OF PANTOPRAZOLE IN DOGS AND RELATIVE BIOAVAILABILITY OF PANTOPRAZOLE FROM ENCAPSULATED ENTERIC-COATED SPHEROID FORMULATIONS

Parameter	20 mg	40 mg	40 mg Encapsulated	40 mg
	Market Tablet Batch A98D015 Pantoprazole Na ^a	Uncoated Tablet Batch 121040 Pantoprazole Na ^b	Enteric Spheroids Batch L20400-185EC Pantoprazole Mg	Encapsulated Enteric Spheroids Batch L20400-192EC Pantoprazole Na
AUC _{0-∞} (ng-hr/mL)	14578 (4779)	17742 (5712)	10175 (3018)	15404 (5154)
C _{max} (ng/mL)	10569 (4258)	11259 (2130)	3356 (897)	6232 (2640)
t _{max} (hr)	2.08 (1.20)	0.46 (0.19)	1.42 (0.66)	1.17 (0.26)
t _{lag} (hr)	1.42 (1.13)	0.00 (0.00)	0.21 (0.19)	0.25 (0.16)
t _{1/2} (hr)	0.60 (0.15)	0.63 (0.11)	0.94 (0.51)	0.77 (0.19)
Relative Bioavailability	--	AUC: 122% ^c C _{max} : 107% ^c	AUC: 70%/57% ^d C _{max} : 32%/30% ^d	AUC: 106%/87% ^d C _{max} : 59%/55% ^d

a: AUC and C_{max} normalized to a 40 mg dose

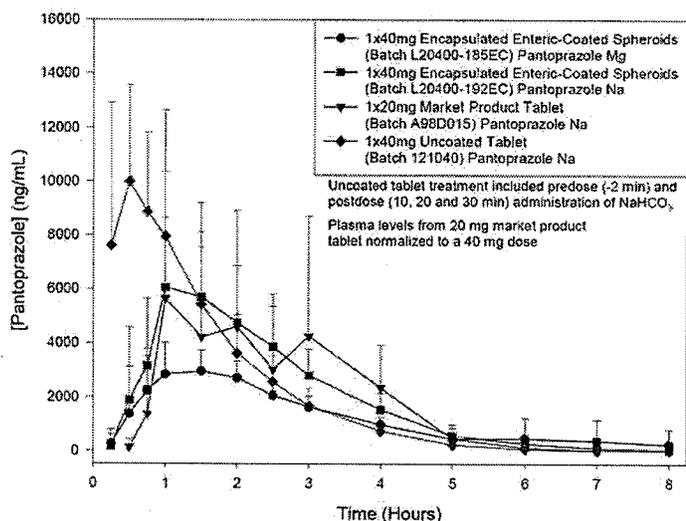
b: Uncoated tablet treatment included pre-dose (-2 min) and post-dose (10, 20 and 30 min) administration of NaHCO₃

c: Relative to Market Product Tablet

d: Relative to Uncoated Tablet

The mean plasma pantoprazole concentrations in dogs receiving the four pantoprazole formulations are shown in the Figure below.

FIGURE 1. MEAN (SD) PLASMA PANTOPRAZOLE LEVELS IN DOGS (N=6)



In summary, the pharmacokinetic parameters and relative bioavailabilities of pantoprazole sodium and pantoprazole magnesium encapsulated enteric-coated spheroids to those from pantoprazole sodium enteric-coated marketed tablet product and an uncoated pantoprazole sodium tablet product were compared in dogs following administration of a single oral dose. The results indicated that pantoprazole magnesium encapsulated enteric-coated spheroids provided lower pantoprazole plasma exposure levels than the marketed

pantoprazole product. The pantoprazole sodium encapsulated enteric-coated spheroids exhibited a mean plasma exposure level similar to that of the marketed tablet product; however, the C_{max} for the spheroid formulation was lower than that of the marketed tablet product. The doses administered were not same for all the formulations. For the marketed pantoprazole product, the dose was 20 mg, and for all other formulations, a 40 mg dose was used. Pharmacokinetic data from the marketed product (administered at 20 mg) was dose-normalized to 40 mg to allow comparison to the other three formulations. Thus, this may not be a direct comparison of bioavailabilities for these formulations.

2.6.6 TOXICOLOGY

No toxicology study reports were submitted.

LABELING:

No changes in the preclinical section of proposed labeling are recommended.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions:

Pantoprazole is a substituted benzimidazole, and it inhibits gastric acid secretion by specific irreversible inhibition of the enzyme, H^+K^+ -ATPase (also known as proton pump) at the surface of the gastric parietal cells. Pantoprazole delayed release tablets (Protonix Tablets) are currently marketed in the U.S. for use in maintenance of healing of erosive esophagitis, for the control of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease (GERD) and for use in pathological hypersecretory conditions including Zollinger-Ellison Syndrome. The sponsor submitted the current NDA for an enteric-coated pantoprazole sodium granules formulation (equivalent to 40 mg pantoprazole) for the same indications. The granules formulation was developed as an alternative to the tablet formulation for administration to patients unable to swallow the tablet.

In the current submission, the sponsor submitted a pharmacokinetic study report in which the relative bioavailabilities of pantoprazole sodium and pantoprazole magnesium enteric-coated spheroids formulations were compared with those of the marketed delayed release tablet product and an uncoated tablet preparation in male beagle dogs following oral administration of a single dose. No other preclinical studies were submitted under the current NDA. The sponsor referred to NDA 20-987, under which the preclinical profiles of pantoprazole sodium have been well-characterized.

The nonclinical pharmacology profiles of pantoprazole show that it is a potent and long-lasting inhibitor of gastric acid secretion. Studies with pantoprazole were conducted to examine its *in vivo* and *in vitro* effects on gastric acid secretion, ulcer prevention and curative activities. Primary and ancillary pharmacology studies conducted with pantoprazole were as follows: gastric acid secretion in rats, gastric acid secretion in dogs, anti-ulcer effects in rats, *in*

in vitro inhibition of H⁺/K⁺-ATPase, and ancillary pharmacology studies relating to central nervous system effects, cardiovascular effects, general pharmacology and miscellaneous effects. The binding of pantoprazole to H⁺/K⁺-ATPase is irreversible in nature, and effectively inhibits acid secretion until new enzyme is synthesized. In vivo studies with pantoprazole administered by the oral or intravenous route to rats demonstrated inhibition of basal acid secretion as well as secretion induced by 2-deoxy-d-glucose, bethanecol and pentagastrin. Oral pantoprazole inhibited or abolished aspirin-, stress- or acidified ethanol-induced gastric mucosal lesions in rats as well as gastric and duodenal ulcers induced by acetic acid. Inhibition of gastric mucosal lesions paralleled inhibition of gastric acid secretion.

Studies to determine the single and repeat-dose pharmacokinetics of pantoprazole were conducted in mice, rats, dogs and monkeys. Plasma C_{max} and AUC values for total radioactivity/and or the parent drug increased with increasing dose, although, generally not in a dose-proportional manner. C_{max} and AUC values for unchanged drug in rats, mice, dogs and monkeys encompassed values in healthy human volunteers receiving a 40 mg (0.8 mg/kg) dose. Plasma AUC values for the parent compound were found to represent a small fraction of the total radioactivity suggesting extensive metabolism. Pantoprazole appeared to undergo extensive first pass metabolism, and bioavailability values displayed high variability. Bioavailability of the parent compound following an oral dose of 5 mg/kg in rats and a 60 mg/kg in dogs were 31% and 44%, respectively. Bioavailability of the parent compound in cynomolgous monkeys following a 5 mg/kg dose was 3.5%. The half-lives of the parent compound in most species were generally <1.0 hr. The bioavailability of an oral therapeutic dose of 40 mg in healthy volunteers ranged from 47.3% to 90.8%. Tissue distribution (rats and monkeys), protein binding (mice, rats and dogs), metabolism (rats, dogs and monkeys) and excretion (mice, rats, dogs and monkeys) studies with pantoprazole sodium were conducted in different animal species. Pantoprazole binding to rat and human serum protein exceeded 95%. Binding with dog serum protein was lower (80 to 90%). Autoradiography studies in rats following oral administration showed that the peak concentrations of the radioactivity were reached in most tissues in 1.0 hr after dosing. The radioactivity in the plasma remained constant from 24 to 96 hours due to association of the radiolabeled material with the red blood cells. In pregnant rats, pantoprazole-related radioactivity crossed the placental barrier, and in lactating rats, radioactivity was secreted in milk. In human liver microsomes, pantoprazole was mainly metabolized by CYP2C19 and CYP3A4. Other studies suggested that CYP2D6, CYP2C9 and CYP2C10 also appeared to play a role in the metabolism of pantoprazole. Pantoprazole acted as a specific inducer of CYP2B1 and CYP2B2 isozymes. Following oral administration of single doses to male dogs, the pantoprazole sodium encapsulated enteric-coated spheroids exhibited a mean plasma exposure (dose normalized) similar from that the marketed tablet product; however, the C_{max} for the spheroid formulation was lower than that of the marketed tablet product (~52%).

The toxicity of pantoprazole was evaluated in acute oral and intravenous studies in mice, rats and dogs, in repeat dose oral studies in rats and dogs, and in repeat dose i.v. studies in rats, dogs and monkeys for up to 1 month. In mice, the maximum non-lethal doses were 750 and 500 mg/kg in males and females, respectively. In rats, the oral maximal non-lethal dose was 700 mg/kg, and the minimal lethal dose was 900 mg/kg for both males and females. In beagle dogs, following oral administration, the maximal non-lethal and minimum lethal doses

were 300 and 1000 mg/kg, respectively. Clinical signs observed in mice, rats and dogs following oral or intravenous pantoprazole included decreased activity and ataxia.

In a 4-week i.v. toxicity study in Sprague-Dawley rats, pantoprazole doses of 0, 1, 5 or 30 mg/kg/day were used. The 30 mg/kg/day dose was identified as the no effect dose. Serum gastrin levels, stomach weights and height of the gastric mucosa were increased in all treatment groups; however, these changes were reversible during a 30-day recovery period. Grimelius-positive-cell (GPC)-areas were increased in male and female pantoprazole treatment groups; although, there was no dose-response relationship. The GPC-area was still increased in the 30 mg/kg/day group at the end of the 30-day recovery period.

In a 4-week oral toxicity study in Sprague-Dawley rats, pantoprazole doses of 0, 1, 5, 20 and 500 mg/kg/day were used. Following the treatment period, selected animals from the control and 500 mg/kg/day groups entered an 8-week recovery period. The 5 mg/kg/day dose could be considered a tolerated dose. Elevated serum gastrin levels were observed in animals receiving doses of ≥ 5 mg/kg/day; however, the gastrin levels of the recovery animals could not be determined due to technical problems. The target organs of toxicity were the stomach, thyroid gland and the spleen. In the fundic region of the stomach, the following changes were observed: an increased incidence of chief cell hyperplasia at doses ≥ 5 mg/kg/day, an increased incidence of parietal cell hyperplasia at ≥ 5 mg/kg/day, and an increased incidence of parietal cell degeneration/vacuolation at doses of ≥ 20 mg/kg/day. Parietal cell hyperplasia and degeneration/vacuolation were still evident in the high dose group at the end of the recovery period. For the thyroid gland in female rats that received 500 mg/kg/day, epithelial cells in the follicle underwent a change in cell morphology from mainly flat follicle cells to mainly cuboidal follicle cells. These changes were not evident at the end of the recovery period. There was evidence of iron depletion in the spleen at ≥ 20 mg/kg/day.

In a 4-week oral toxicity study in Sprague-Dawley rats, pantoprazole doses of 1, 5 and 500 mg/kg/day were used. Selected animals from the control and high dose groups were left untreated for an 8-week recovery period. This study was performed due to problems in measuring plasma gastrin levels of the recovery animals in the previous study. Treatment-related increases in the plasma gastrin levels were observed in rats that received doses ≥ 1 mg/kg/day. At the end of the first week of recovery period, serum gastrin levels were still significantly higher in high dose females. After 4 and 8 weeks of the recovery period, serum gastrin levels returned to normal.

In a 3-month oral toxicity study, female rats of three different strains (Sprague-Dawley, Wistar and Fischer; 52-57 weeks of age) received pantoprazole at doses of 0, 0.8 and 4 mg/kg/day. The 0.8 mg/kg/day dose could be considered a tolerated dose. Histopathological examination of the stomach, liver, lungs and thyroids was performed for all groups. The stomach, liver and the thyroid gland were the target organs of toxicity. In the gastric fundus, parietal cell hyperplasia, foveolar hyperplasia, chief cell hyperplasia and atypical eosinophilic chief cells were observed at a dose of 4 mg/kg/day for all strains of rats. Foveolar hyperplasia and chief cell hyperplasia were also observed for Wistar and Fischer rats at a dose of 0.8 mg/kg/day. The number of Grimelius-positive cells increased dose-dependently for all rat strains. Peribiliary inflammation and bile duct proliferation were observed in Sprague-Dawley

and Wistar rats that received a 4 mg/kg/day dose. For the thyroid gland, follicular epithelium was slightly increased in Wistar rats that received the 4 mg/kg/day dose. Proliferation of c-cells was evident in all strains at 4 mg/kg/day, and in Wistar rats at 0.8 mg/kg/day.

In a 6-month oral toxicity study in Sprague-Dawley rats, pantoprazole doses of 0, 0.8, 4, 16 and 320 mg/kg/day were used. Additional animals from the control and high dose groups were entered an 8-week recovery period at the end of the treatment period. The 4 mg/kg/day dose could be considered a tolerated dose, given the changes in the stomach were related to the pharmacological actions of the drug. During the treatment period at all sampling times, serum gastrin levels were elevated at doses ≥ 4 mg/kg/day. During the recovery period, gastrin levels were elevated in the 320 mg/kg/day group at week 1, but not at week 8. The stomach, liver, thyroid gland and the spleen were the target organs of toxicity. Increased incidences of chief cell hyperplasia in the fundic region of the stomach and an increased incidence of chief cell atrophy were observed at ≥ 0.8 mg/kg/day. An increased incidence of parietal cell degeneration/vacuolation and cell infiltrates was observed at 320 mg/kg/day, and an increased incidence of parietal cell hyperplasia was observed at 4 and 16 mg/kg/day. Parietal cell hyperplasia and inspissated secretory products persisted through the recovery period. Centrilobular swelling of hepatocytes was observed in male rats at ≥ 0.8 mg/kg/day, and in female rats at 320 mg/kg/day. Bile duct hyperplasia was observed in male rats at 320 mg/kg/day. Hepatocellular adenoma was observed in one (of 24) male rat treated with 320 mg/kg/day. Epithelial cells of the thyroid follicles underwent a change in cell morphology to cuboidal to columnar features for female rats at 16 and 320 mg/kg/day. A C-cell adenoma in thyroid was present in one (of 24) female rats receiving the 16 mg/kg/day dose. Males receiving the 320 mg/kg/day dose had depletion of iron levels in the spleen, and persisted through the recovery period.

In a 12-month oral toxicity study in Sprague-Dawley rats, pantoprazole doses of 0, 5, 50 and 300 mg/kg/day were used. Additional rats were included in the 0 and 5 mg/kg/day groups for a 9-month recovery period following treatment. The 5 mg/kg/day dose could be considered a tolerated dose. Serum gastrin, cholesterol and triglyceride levels were elevated at doses ≥ 5 mg/kg/day. The stomach, liver, thyroid gland, spleen and kidney were the target organs of toxicity. Increased height of the fundic mucosa, fundic gland ectasia, eosinophilic chief cells, mixed infiltratory cell infiltrates (fundus), mild fibrosis of the lamina propria and hyperplasia of chromogranin-positive cells (fundus) were observed in the stomach at ≥ 5 mg/kg/day. The diffuse ECL cell index was increased at a dose of 5 mg/kg/day; however, the index decreased with increasing dose. In contrast, focal hyperplasia was more prominent at 300 mg/kg/day than at 5 mg/kg/day. Centrilobular hepatocellular hypertrophy was observed at ≥ 5 mg/kg/day, and hepatocellular necrosis was observed at ≥ 50 mg/kg/day. Thyroid follicular cell hypertrophy and reduced hemosiderin in the spleen were observed at ≥ 50 mg/kg/day. For the kidney, the incidence of mild to severe nephropathy was increased at doses of ≥ 50 mg/kg/day, and the incidence of urothelial hyperplasia was increased at 300 mg/kg/day. At the end of the recovery period, a malignant neuroendocrine cell tumor (fundus) was observed in one (of 11) female rat at 5 mg/kg/day. Gastric effects induced by pantoprazole at 5 mg/kg/day were not reversible.

In a 10-day oral toxicity study in beagle dogs (one animal/sex/group), pantoprazole was administered as enteric-coated tablets at doses of 75 and 100 mg/kg/day, or as uncoated tablets at doses of 50, 75, 100 and 150 mg/kg/day. For the surviving male dog receiving 100 mg/kg enteric-coated tablets, the dose was reduced to 75 mg/kg/day on day 5. The following dogs died or were sacrificed moribund during the treatment period: females receiving 75 and 100 mg/kg enteric-coated tablets; the male and female receiving 100 mg/kg uncoated tablets, and the female receiving 50 mg/kg uncoated tablets. Necropsy examinations of these animals showed evidence of pulmonary edema. Histopathological examinations of the lungs of these animals revealed effusion of fluid into the pulmonary alveoli. Findings included foamy alveolar macrophages and eosinophilic material in alveoli suggestive of proteinaceous fluid. Animals receiving 75 and 100 mg/kg uncoated tablets also had periobronchiolar/perivascular edema and edema of the mediastinal structures (e.g., thymus, heart/pericardium, esophagus). Dogs sacrificed after 10 days of treatment showed minimal to moderate parietal cell vacuolation in the stomach.

In a 30-day oral toxicity study in beagle dogs, groups of animals were administered pantoprazole at doses of 0, 7.5, 15, 30 and 100 mg/kg/day. There were 5 dogs/sex/group. Two dogs/sex/group were sacrificed after 5 days and examined specifically for pulmonary changes. The 15 mg/kg/day dose could be considered a tolerated dose, and the stomach and lungs were the target organs of toxicity. Alveolar foamy macrophages were detected in the 100 mg/kg/day group on day 5, but no such changes were observed on day 30. Following treatment for 30 days, parietal cell vacuolation in the stomach was detected at doses \geq 15 mg/kg/day. Based on lung lavage content of protein and foamy alveolar macrophages, lung injury appeared to be most severe 3 to 5 days after the start of treatment, with resolution of changes occurring with continued treatment.

In a 6-month oral toxicity study in beagle dogs, groups of animals received pantoprazole at doses of 0, 15, 45 and 90 mg/kg/day. Additional dogs were included in the high dose group for a 4-week recovery period following treatment. However, no control recovery group animals were included in study. In order to minimize lung toxicity at doses of 45 and 90 mg/kg/day, doses were elevated in an incremental fashion. When the final dose was reached, the 6-month treatment period was started. Due to clinical signs observed at doses of 45 and 90 mg/kg/day, these doses were reduced to 30 and 60 mg/kg/day, respectively. Increased gastrin levels were observed in all treated male and female dogs. Increased cholesterol and triglyceride levels were observed in the 45/30 and 90/60 mg/kg/day groups. The stomach and the liver were the target organs of toxicity. Inflammatory cell infiltrate in the cardiac and fundic region of the stomach, and dilated crypts in the stomach, duodenum, cecum, colon and rectum were observed at doses of \geq 15 mg/kg/day. Brown pigment accumulation in the liver was observed at 90/60 mg/kg/day, and was still present at the end of the recovery period. Inspissated bile was observed in all drug treated groups.

In a 1-year oral toxicity study, beagle dogs received pantoprazole (non-enteric coated tablets in capsules) at doses of 0, 2.5, 15 and 60 mg/kg/day. The highest tested dose was achieved by dose escalation. The 2.5 mg/kg/day dose could be considered a tolerated dose. One male dog from the 60 mg/kg/day group had drug-induced pulmonary edema, which was resolved by the 7th day of the study. One male dog from the 15 mg/kg/day group died of

pulmonary edema on day 4. A thiourea-like metabolite of pantoprazole (B8401-026) is thought to be responsible for induction of pulmonary edema following administration of pantoprazole to dogs. Pulmonary edema appears to be transient and tolerance develops with multiple dosing. Final body weights on day 364 were suppressed by >10% for males and females at doses \geq 15 mg/kg/day. At the end of the treatment period, serum cholesterol levels were increased at all dose levels, and serum triglyceride levels were increased for all male treatment groups. Serum gastrin levels were elevated in all male and female treatment groups. The stomach, thyroid gland, gall bladder and lungs were the target organs of toxicity. Histopathological changes in the stomach at doses of \geq 2.5 mg/kg/day were as follows: increased height of fundic mucosa, increased fundic mucosal folding, dilation of fundic glands, cellular debris in lumen of dilated glands and increased chromogranin-positive cells in the fundic region. Additional findings at doses \geq 15 mg/kg/day included vacuolation of parietal cells. For the thyroid gland, hypertrophy of the follicular cells was observed for male dogs at doses \geq 15 mg/kg/day and for female dogs at 60 mg/kg/day. For the gall bladder, crypt dilation was observed for all female treatment groups and one male dog at 15 mg/kg/day.

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The genotoxic potential of pantoprazole was evaluated in a battery of *in vitro* and *in vivo* genotoxicity assays. *In vitro* studies included the bacterial reverse mutation assay, human lymphocyte chromosomal aberration assay, Chinese hamster ovary cell hypoxanthine guanine phosphoribosyl transferase (CHO/HGRPT) forward mutation assay, unscheduled DNA synthesis assay with rat hepatocytes, AS52/GPT mammalian cell-forward gene mutation assay, thymidine kinase mutation test with mouse lymphoma L5178Y cells, and malignant transformation assay with C3H M2 fibroblasts. *In vivo* studies included the mouse micronucleus assay, the rat bone marrow chromosomal aberration assay, measurement of DNA binding with rats, and ^{32}P -postlabeling experiment with liver DNA. Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGRPT 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* bacterial reverse mutation assay (Ames assay), the 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.

The genotoxic potential of the thiol metabolite of pantoprazole (B8401-026) was assessed *in vitro* in the bacterial reverse mutation assay and malignant transformation assay in C3H M2-fibroblasts, and *in vivo* in the mouse micronucleus assay. B8401-026 was negative in the bacterial reverse mutation assay and malignant transformation assay in C3H M2-fibroblasts. In the first mouse micronucleus assay, 250 mg/kg B8401-026 at the 48 hr sampling time produced a positive response. In the second mouse micronucleus test, doses of 50 to 250 mg/kg with sampling times of 36 to 48 hr produced a negative response. Thus, the thiol metabolite of pantoprazole (B8401-026) potentially possesses clastogenic activity.

The carcinogenic potential of pantoprazole was evaluated in 24-month oral studies in mice (B6C3F1) and two strains of rats (Sprague-Dawley and Fischer 344), and in a 26-week oral study on p53 \pm heterozygous mice. In addition, studies to assess the potential for tumor promotion were conducted. In a 24-month carcinogenicity study, Sprague-Dawley rats were

treated orally with pantoprazole at doses of 0.5 to 200 mg/kg/day. In the gastric fundus, treatment of 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 of 50 and 200 mg/kg/day produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

In a 24-month carcinogenicity study, Fischer rats were treated orally with pantoprazole doses of 5 to 50 mg/kg/day. 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. However, 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. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

A 26-week p53[±] transgenic mouse carcinogenicity study was not positive.

Pantoprazole was evaluated in fertility and general reproductive performance studies in rats, developmental toxicity studies in rats and rabbits, and peri- and post- natal development studies in rats.

In an oral Segment I fertility and general reproductive performance study, male Sprague-Dawley rats received pantoprazole (by gavage) at doses of 0, 5, 50 and 500 mg/kg/day. Pantoprazole at oral doses \leq 500 mg/kg/day had no effect on fertility and reproductive performance of male rats. Body weight gain was impaired by 12% for male rats at the 500 mg/kg/day dose. In the first mating trial, the fertility index was low (54-80%) for control and all treatment groups. In a second mating trial after 112 days of treatment, fertility indexes ranged from 83 to 96% in the control and treatment groups. The mating index ranged from 92 to 100% for control and treatment groups in both trials.

In an oral Segment I fertility and general reproductive performance study in female rats, pantoprazole was administered at doses of 0, 50, 150 and 450 mg/kg/day from 14 days prior to mating through the gestation and lactation periods. Pantoprazole at oral doses up to 450 mg/kg/day had no effect on the fertility and general reproductive performance of female rats.

In an oral Segment II teratology study, pregnant female Sprague-Dawley rats received pantoprazole (oral gavage) at doses of 0, 50, 150 and 450 mg/kg/day from days 6 through 15 of gestation. Pantoprazole at oral doses up to 450 mg/kg had no teratogenic effects in rats. Body weight gain was impaired by 12%, and prostration, eating bedding material and piloerection were observed at the 450 mg/kg dose. An increased pre-implantation loss was observed for dams receiving the 450 mg/kg dose. There were no treatment related external or visceral

malformations or variations. No treatment related skeletal malformations were observed in any group; however, a dose-dependent delay of ossification for fetal cranial bones was observed.

In a second oral Segment II teratology study, pregnant female Sprague Dawley rats received pantoprazole at doses of 0, 5, 15 and 50 mg/kg/day from days 6 through 15 of gestation. The study was conducted to identify an oral no effect dose for delay of ossification for fetal cranial bones that was observed in an earlier Segment II teratology study. Pantoprazole at doses \leq 50 mg/kg/day produced no evidence of teratogenic effects. Skeletal examination of fetuses revealed that the 5 mg/kg/day dose had no effect on the ossification of bones in the skull. At doses of 15 and 50 mg/kg/day, there was evidence of incomplete ossification of cranial bones.

In an oral Segment II teratology study in rabbits, pregnant females received pantoprazole by intubation at doses of 0, 2.5, 10 and 40 mg/kg/day from days 6 through 18 of gestation. Pantoprazole at oral doses up to 40 mg/kg/day was not teratogenic in rabbits. No treatment related external, skeletal and visceral abnormalities were seen in any group, except that delayed dental growth was observed for the 40 mg/kg/day dose.

In an oral Segment III perinatal and postnatal development study in Sprague Dawley rats, pregnant animals were administered (gavage) pantoprazole at doses of 0, 1, 3 and 30 mg/kg/day from day 15 of gestation to day 21 after parturition. Pantoprazole at oral doses up to 30 mg/kg/day had no significant effects on perinatal and postnatal development in rats. No treatment related effects were seen in the F1 pups during the post-natal period except that the body weight gain of pups at 30 mg/kg/day was significantly reduced (19-22%) during the lactation period as compared with the control values. This retardation of body weight gain was still evident in male offspring until 12 weeks of age. At the end of 12 weeks, the body weights of male pups from the high dose group were about 8% lower than that observed in pups from the control group. Developmental and reproductive performances were comparable in all groups.

In a special toxicology study, the relationship between pulmonary toxicity and systemic exposure to the thiol metabolite of pantoprazole (B8401-026/L \rightarrow 97165) was examined in beagle dogs that received either pantoprazole at i.v. doses of 0, 15 and 50 mg/kg/day (the high dose was reduced to 40 mg/kg/day on day 2) or the thiol metabolite at i.v. doses of 2.5, 5 and 15 mg/kg/day for 5 days. Protein content in the lung fluid was elevated for all treatment groups. Moderate vacuolation of macrophage cytoplasm, foamy alveolar macrophages and increased lung water content were observed with pantoprazole at 50/40 mg/kg/day and the thiol metabolite at 5 and 15 mg/kg/day. Same processes were occurring following administration either pantoprazole or its thiol metabolite and that a dose-response relationship existed with both compounds. These findings seem to support the concept that pantoprazole-induced pulmonary toxicity might be associated with the thiol metabolite.

Pantoprazole administered by oral gavage at a dose of 700 mg/kg/day for 14 days had a mitogenic action in male and female Sprague Dawley rats as reflected by increased hepatic DNA levels. Pantoprazole doses of 200 and 500 mg/kg/day did not produce statistically significant increases in hepatic DNA levels.

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Pantoprazole was negative in the guinea pig maximization test, and in both active systemic anaphylaxis and passive cutaneous anaphylaxis tests in guinea pigs. No delayed hypersensitivity reaction was observed in guinea pigs treated with the thiol metabolite of pantoprazole (B8401-026).

Following intramuscular injection of pantoprazole to rats, no significant differences in the incidences or severity of necrosis or local signs of tolerance were observed between the treatment and control groups. No signs of local intolerance were observed in rabbits that received a single intravenous injection of a 0.4% pantoprazole solution. A single intravenous, paravenous or intraarterial injection of 4% pantoprazole (free acid) into the ear did not produce local irritation in rabbits. Pantoprazole and its thiol metabolite had low potentials for dermal irritation in rabbits. There were no signs of local irritancy following intravenous and paravenous administration of pantoprazole to one male beagle dog.

The *in vitro* effects of pantoprazole on red blood cells were examined in two studies. Incubation of human red blood cells with 10 mg/ml pantoprazole for 2 min did not produce any significant hemolysis; however, incubation for 30 min produced 4 to 17% hemolysis as compared to 0 – 7.0% for the vehicle. Pantoprazole at concentrations of 3×10^{-8} to 3×10^{-5} M had no effect on hypotonic hemolysis of human, dog or rat red blood cells. Pantoprazole, at a concentration of 3×10^{-4} M, reduced the hypotonic hemolysis of dog and rat erythrocytes by 15-20% and human erythrocytes by 30%.

Recommendations: The preclinical toxicology studies conducted with pantoprazole support the safety of pantoprazole granules at the proposed doses.

Suggested labeling: No changes in the preclinical section of the current labeling of Protonix (pantoprazole sodium) Delayed Release Tablets are recommended.

Signatures:

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

cc: list:

NDA

HFD-180

HFD-181/CSO

HFD-180/Dr. Chakder

HFD-180/Dr. Choudary

R/D Init.: J. Choudary 3/8/07

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/s/

Sushanta Chakder
3/9/2007 09:25:17 AM
PHARMACOLOGIST

Jasti Choudary
3/9/2007 11:55:35 AM
PHARMACOLOGIST