

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20988

PHARMACOLOGY REVIEW

NDA 20,988

Sponsor: Wyeth Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-8299

REVIEW # 1

Reviewer: Timothy W. Robison, Ph.D
Pharmacologist, HFD-180

APR 30 1999

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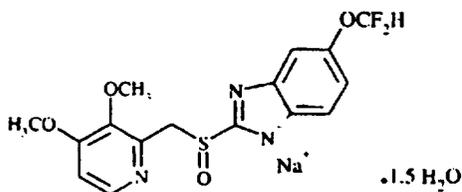
Date of Review: April 22, 1999

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

ORIGINAL SUMMARY

Drug: Pantoprazole (PROTONIX™ I.V.); Sterile Pantoprazole Sodium

Chemical Name and Structure: sodium 5-(difluoromethoxy)-2-[[3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sesquihydrate



Molecular Formula: C₁₆H₁₄F₂N₃NaO₄S x 1.5 H₂O

Molecular Weight: 432.4

Formulation: PROTONIX™ I.V. is supplied as a freeze-dried powder in a clear glass vial fitted with a rubber stopper and crimp seal containing the equivalent of 40 mg of pantoprazole. PROTONIX™ I.V. is reconstituted with 10 mL of 0.9% Sodium Chloride Injection, USP. The reconstituted solution of PROTONIX™ I.V. is in the pH range of 9.0 to 10.0.

Active Ingredient	mg/vial	Input/vial
Pantoprazole sodium	42.3 mg	45.1 mg

Inactive Ingredients	Input/vial
Water for Injection, USP	--
Nitrogen, NF	--

Category: Gastric parietal cell H⁺/K⁺-ATPase inhibitor; Proton pump inhibitor.

Related Drugs/INDs/NDAs/MFs: IND [redacted] of SmithKline Beecham of Philadelphia, PA and Byk Gulden GmbH of Konstanz, Germany; IND [redacted] from Wyeth-Ayerst Research of Philadelphia, PA; and NDA 20,987 from Wyeth-Ayerst Research of Philadelphia, PA.

Proposed Marketing Indication: PROTONIX™ I.V. is indicated for short term gastric acid suppression in gastroesophageal reflux disease (GERD) patients who are unable to take oral medication. The duration of treatment will be ≤7 days.

Dose: The recommended adult intravenous dose is one vial containing the equivalent of 40-mg pantoprazole given daily for gastric acid suppression in patients with GERD who are unable to take the oral dosage.

APPEARS THIS WAY
ON ORIGINAL

Preclinical Studies and Testing Laboratories:

STUDY	GTR #	TESTING LABORATORY	DRUG BATCH
PHARMACOLOGY^{A,R,S}:			
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION:			
ABSORPTION			
Mouse			
Rat			
Pharmacokinetics of pantoprazole, omeprazole, and lansoprazole following a single intravenous dose ^R .	31305		
Stereoselective chiral inversion of pantoprazole enantiomers ^R .	32139		
Dog			
Pharmacokinetics of pantoprazole and its sulfone metabolite in the dog following single and repeated oral and intravenous doses ^R .	31546		
Monkey			
Absorption of ¹⁴ C-pantoprazole following oral and intravenous administration ^R .	31549		
DISTRIBUTION			
¹⁴ C-pantoprazole binding to rat, dog, and human serum proteins ^{R,S} .	31194		
In vitro binding of pantoprazole, omeprazole, and lansoprazole in human, rat, and mouse plasma ^{R,S} .	27796		
Estimation of plasma:whole blood concentration ratios in vitro using rat, dog, and human blood ^R .	31199		
Rat			
Whole body autoradiographic study after a single oral or intravenous administration of [¹⁴ C-Pyridyl]-pantoprazole ^A .	31326		
Melanin binding of radioactivity in male pigmented rats following intravenous or oral administration of ¹⁴ C-pantoprazole at 5 mg/kg (¹⁴ C at 2-position of benzimidazole ring) ^R .	31198		
Whole body autoradiographic study on the distribution of radioactivity following intravenous or oral administration of ¹⁴ C-pantoprazole (¹⁴ C at 2-position of benzimidazole ring) ^R .	31223		
Transplacental transport and mammary glandular passage of ¹⁴ C-pantoprazole (¹⁴ C at 2-position of benzimidazole ring) ^A .	31203		
Quantitative distribution of radioactivity after a single intravenous administration of ¹⁴ C-pantoprazole (¹⁴ C at 2-position of benzimidazole ring) ^R .	31224		
Distribution of [¹⁴ C-Pyridyl]-pantoprazole in organs and tissues of male rats after a single intravenous administration ^A .	31314		
Monkey			
Distribution of ¹⁴ C-pantoprazole ^R .	31549		

METABOLISM			
Enzyme Inhibition and Induction-In Vitro			
Inhibition of hydroxylation of lonazolac (Cytochrome P450 Dependent Reaction) ^A .	31210		
Interaction with ethylmorphine demethylase activity (Cytochrome P450) in rat liver microsomes ^R .	31211		
Influence on 7-ethoxycoumarin dealkylase activity (Cytochrome P450) in rat liver microsomes ^R .	33324		
Effect of 7-ethoxycoumarin dealkylase activity-Cytochrome P450 in rat liver microsomes ^A .	31209		
Interaction with lonazolac in human microsomes ^R .	31217		
Interaction of omeprazole, pantoprazole, and another proton pump inhibitor with rat liver cytochrome P450 in vitro ^R .	31206		
An evaluation of the CYP1A induction potential using primary rat hepatocytes and comparison with other proton pump inhibitors ^R .	31189		
An evaluation of the Cytochrome P450 induction potential using primary rat hepatocytes and comparison with other proton pump inhibitors ^R .	32138		
Identification of Cytochrome P450 isozymes involved in the metabolism of pantoprazole with human liver microsomes ^A .	23/96 K1		
Biotransformation of pantoprazole in human microsomes. Identification of P450 isozymes by selective inhibitors ^A .	31216		
Enzyme Inhibition and Induction-In Vivo			
Interactions of cimetidine, omeprazole, lansoprazole, or pantoprazole with diazepam in rats ^A .	31212		
Effects on the drug-metabolizing enzyme system in rat liver ^A .	31544		
Rats and Dogs-Metabolism Characteristics and Metabolites			
Biotransformation of ¹⁴ C-pantoprazole in selected organs of the rat ^R .	31302		
Metabolism of ¹⁴ C-pantoprazole in rats following a single oral or intravenous administration ^{A,R} .	31202		
Metabolism of ¹⁴ C-pantoprazole in rats following a single oral or intravenous administration ^A .	31325		
Metabolism of ¹⁴ C-pantoprazole in rat and dog ^R .	31201		

EXCRETION			
Mouse			
Excretion of radioactivity in mice after oral administration of ¹⁴ C-pantoprazole ^A .	31315		
Rat			
Balance, excretion, and pharmacokinetic study in male rats following oral and intravenous administration of [¹⁴ C-Pyridyl]-pantoprazole ^A .	31310		
Kinetics in blood and balance excretion in rats after intravenous dosing with ¹⁴ C-pantoprazole ^R .	31218		
Biliary excretion and metabolism of ¹⁴ C-pantoprazole in rats ^A .	31328		
Dog			
Balance excretion and pharmacokinetic study in male beagle dogs following oral and intravenous administration of ¹⁴ C-pantoprazole ^R .	31191		
Monkey			
Excretion of radioactivity following oral and intravenous administration of ¹⁴ C-pantoprazole ^R .	31549		
TOXICOLOGY:			
ACUTE TOXICITY IN MICE, RATS, AND DOGS			
Acute toxicity of pantoprazole in mice, rats, and dogs following intravenous administration ^{A,R,S} .	31633 31637 31638 31640 32136 31650 31643	Byk Gulden Konstanz, Germany	489065 K23/144 K23/144 589085 294160 513150 033927 349235 589085
Acute intravenous toxicity of (+)Enantiomer in mice ^A .	31644	Byk Gulden Konstanz, Germany	
Acute intravenous toxicity of (-)Enantiomer in mice ^A .	31645	Byk Gulden Konstanz, Germany	
Acute oral toxicity of the thiol metabolite in rats ^A .	32262		
Acute intravenous toxicity of B8810-04 in mice and rats ^R .	31648 31649	Byk Gulden Konstanz, Germany	K33/141-1
RAT			
Subacute Toxicology			
Intravenous Route of Administration			
4-Week intravenous toxicity study ^A .	31901	Byk Gulden Konstanz, Germany	K19/271-3
4-Week intravenous toxicity study-local tolerance ^A .	32004	Byk Gulden Konstanz, Germany	K21-120A
4-Week intravenous toxicity study with unstressed batch ^R .	32911	Byk Gulden Konstanz, Germany	293610
4-Week intravenous toxicity study with stressed batch ^R .	32910	Byk Gulden Konstanz, Germany	195220
4-Week intravenous toxicity study with N-methylpantoprazole (B8810-04) ^R .	32006	Byk Gulden Konstanz, Germany	Zi20/107A

DOG			
Subacute Toxicology			
Intravenous Route of Administration			
2-Week toxicity study using oral and intravenous routes-special emphasis on toxic effects on the eye and ear ^R .	32001	Byk Gulden Konstanz, Germany	BY1023-20-1-1; Ch.B.: 513150
30-Day intravenous toxicity ^{A,R} .	31904 31193	SmithKline&French Research Ltd. Herts, UK	3 and 4
4-Week continuous intravenous infusion toxicity study ^R .	32002	-Byk Gulden Konstanz, Germany	513150
CARCINOGENICITY			
Mouse			
2-Year oral carcinogenicity study in B6C3F1 mice ^A .	31899	Byk Gulden Hamburg, Germany	399175
Rat			
2-Year oral carcinogenicity study in Sprague Dawley rats ^A .	31282		299155/89 PD 324, 399-175/89 PD 341/1, and 399- 175/89 PD 341/2
Two-year oral carcinogenicity study in Fischer 344 rats ^{A,R} .	31898 31545	Byk Gulden Hamburg, Germany	500-205
Study for assessing the tumor promoting activity of pantoprazole in stomach and forestomach of Sprague Dawley rats ^R .	33036		0295220000
Study for assessing the tumor promoting activity of pantoprazole in liver and thyroid of Sprague Dawley rats ^R .	33037		0295220000
REPRODUCTIVE TOXICOLOGY:			
Rats			
Oral Segment I fertility and reproductive performance study in male rats ^S .	32063		58905-88PD477
Oral Segment I fertility and reproductive performance study in female rats ^S .	32062		58905-88PD477
Intravenous Segment II teratology study in rats ^S .	32031	Byk Gulden Hamburg, Germany	K23/161
Rabbits			
Intravenous Segment II teratology study in rabbits ^S .	32033	Byk Gulden Hamburg, Germany	579-015
Rats			
Oral Segment III perinatal and postnatal development study in rats ^A .	32081		589085- 88PD480
GENOTOXICITY:			
Studies with Pantoprazole.			
Bacterial reverse mutation assay with pantoprazole ^S .	32058		4
Metaphase chromosomal analysis of human lymphocytes cultured in vitro ^S .	32042		4
Chromosomal aberration assay in human whole blood lymphocytes with pantoprazole ^A .	32046 32253		0494180000
Chromosomal aberration assay in human lymphocytes in vitro with pantoprazole ^R .	32044	Byk Gulden Konstanz, Germany	029522000

Mutagenic potential of pantoprazole in Chinese hamster Ovary/HGPRT Locus Assay ^S .	32057		4
Unscheduled DNA synthesis in primary hepatocytes ^A .	32055		109-195
AS52/GPT mammalian cell-forward gene mutation assay with pantoprazole ^A .	32048		0494180000
Cell mutation assay at the thymidine kinase locus in mouse lymphoma L5178Y cells with pantoprazole ^A .	32047		0494180000
Malignant transformation assay with pantoprazole in C3H-M2 mouse fibroblasts in vitro ^A .	32053		500205
In vitro cell transformation assay using Syrian hamster embryo cells ^A .	32051		500205
Mouse micronucleus test with pantoprazole ^S .	32056		4
Mouse micronucleus test with pantoprazole ^A .	32054		109195
Bone marrow chromosomal aberration assay in Sprague Dawley rats with pantoprazole ^A .	32049		0494180000
Potential for DNA binding of pantoprazole ^A .	32052		500205
4-Week oral toxicity study with pantoprazole, omeprazole, and lansoprazole in rats-hepatotoxic effects. Includes a ³² P-postlabeling study with hepatic DNA ^R .	32977	-Byk Gulden Konstanz, Germany	
Studies with the Thiol Metabolite of Pantoprazole (B8401-026).			
Bacterial reverse mutation assay with the thiol metabolite of pantoprazole ^A .	32256	Byk Gulden Konstanz, Germany	200085
Mouse micronucleus test with the thiol metabolite of pantoprazole ^A .	32252	Byk Gulden Hamburg, Germany	200085
Repeat Mouse micronucleus test with the thiol metabolite of pantoprazole ^A .	32251	Byk Gulden Hamburg, Germany	292109
Malignant transformation assay with the thiol metabolite of pantoprazole ^R .	32254		
Cell transformation assay using Syrian hamster cells with the thiol metabolite of pantoprazole ^R .	32255		292109
Studies with B8810-044.			
Bacterial reverse mutation assay with N-methyl-pantoprazole (B8810-044).	32045	-Byk Gulden Konstanz, Germany	Zi20/107A
SPECIAL TOXICITY STUDIES:			
PULMONARY TOXICITY			
Rat			
The effect of pantoprazole, omeprazole, and the thiol metabolite of pantoprazole on the lung after intravenous administration to rats ^S .	31983 and 31982	Byk Gulden Konstanz, Germany	
Pulmonary toxicity of the thiol metabolite of pantoprazole in male rats ^A .	32260		

Dog			
Comparison of toxicological response and pharmacokinetic behavior of Fisons and Interfauna dogs to intravenous and oral treatment with pantoprazole.	32137		
5-Day intravenous toxicity to establish dose/response relationships for effusion of fluid into pulmonary alveoli following intravenous administration of pantoprazole ^R .	31987	-Byk Gulden Konstanz, Germany	4
5-Day Intravenous Pulmonary Toxicity Study of pantoprazole and the thiol metabolite of pantoprazole in dogs ^S .	31985		589085- 88PD477
EFFECTS ON EYES			
Monkey			
28-Day intravenous electroretinographic study	32005 and 31188	-Byk Gulden Konstanz, Germany	0296300000
ANTIGENICITY/SENSITIZATION STUDIES			
Guinea pig			
Guinea pig maximization test ^S .	31995	Byk Gulden Pharmaceuticals	
Active systemic anaphylaxis and homologous passive cutaneous anaphylaxis tests in guinea pigs ^S .	32029		293140
Guinea pig maximization test with thiol metabolite of pantoprazole ^A .	32259	Byk Gulden Pharmaceuticals	
LOCAL TOLERANCE STUDIES			
Rat			
Local toxicity after intramuscular administration ^R .	31991 and 31998	Byk Gulden Konstanz, Germany	4F
Local toxicity of pantoprazole lyophilisate after intramuscular injection ^A .	32024	Byk Gulden Hamburg, Germany	013927
Local toxicity of pantoprazole lyophilisate after intramuscular injection ^A .	32028	Byk Gulden Hamburg, Germany	425-623
Rabbit			
Local toxicity after a single intravenous injection ^R .	31990 and 31997	Byk Gulden Konstanz, Germany	3 and 4F
Local toxicity after a single paravenous injection ^R .	31988	Byk Gulden Konstanz, Germany	4F
Local toxicity after a single intraarterial injection ^R .	31989 and 31996	Byk Gulden Konstanz, Germany	3 and 4F
Local toxicity of pantoprazole lyophilisate after a single intravenous, paravenous or intra-arterial injection ^A .	32027	Byk Gulden Hamburg, Germany	425623
Local toxicity of pantoprazole lyophilisate after a single intravenous, paravenous or intra-arterial injection ^A .	32039	Byk Gulden Hamburg, Germany	013927

Acute dermal irritation ^A .	32026	Byk Gulden Hamburg, Germany	
Acute dermal irritation with thiol metabolite ^A .	32257	Byk Gulden Hamburg, Germany	
Acute eye irritation test with thiol metabolite ^A .	32258	Byk Gulden Hamburg, Germany	
Dog			
Acute intravenous and perivenous irritancy study ^R .	31993	-Byk Gulden Hamburg, Germany	Formula 16
IN VITRO EFFECTS ON RED BLOOD CELLS			
In vitro human and canine red cell hemolysis study ^R .	31994	-Byk Gulden Hamburg, Germany	3
Effect on membrane stability of human, rat, and dog erythrocytes ^R .	31992	Byk Gulden Hamburg, Germany	K23/161

A. Study reviewed by Dr. Tanveer Ahmad under IND [redacted] Amendment #015 dated October 20, 1993, Amendment #016 dated January 11, 1994, and Amendment #019 dated February 25, 1994 (Document Room Date, August 10, 1994), IND Amendment #24 dated March 29, 1996, Amendment #027 dated June 7, 1996, and Amendment #028 dated June 7, 1996 (Document Room Date, July 9, 1996), and the Initial Submission of IND [redacted] dated December 10, 1996 (Document Room Date, May 14, 1997).

R. Study reviewed by Dr. Timothy W. Robison under NDA 20,987.

S. Study reviewed by Dr. Ching-Long Joseph Sun under the Initial Submission of IND [redacted] dated September 13, 1990 (Document Room Date, November 9, 1990).

For summaries of studies listed above, refer to NDA 20,987 from Wyeth-Ayerst Research of Philadelphia, PA., (dated April 20, 1999).

PROPOSED TEXT OF THE LABELING FOR PANTOPRAZOLE.

Evaluation: The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998).
The text does not accurately report the findings of preclinical toxicology studies.

Proposed Version:

↓ **Sponsor's Version:**

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Evaluation: The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998). The text does not accurately report the findings of carcinogenicity and genotoxicity studies. The sponsor conducted the SHE cell transformation assay at pH 7.2. Recent studies (Kerckaert et al. Mutation Research 356: 65-84, 1996 and LeBoeuf et al. 356: 85-127, 1996) have demonstrated significant advantages of conducting this assay at pH 6.70 as compared to higher pH values (pH 7.10-7.35). These advantages include reduction of the influence of SHE cell isolates and fetal bovine serum lot variability on the assay, an increase in the frequency of chemically-induced morphological transformation (MT) compared to controls, and an increased ease in scoring the MT phenotype. Conducting the assay at pH 6.70 can greatly increase reproducibility and the predictive value of the assay. The results obtained by the sponsor with pantoprazole in the SHE cell assay must be considered highly questionable. Thus, the assay cannot be considered valid. Results from the Segment I fertility and reproductive performance studies in male and female rats were not included.

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pages of trade

secret and/or

confidential

commercial

information

Draft.

Evaluation: The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998). The observed delays in fetal skeletal ossification were variations, which have no effect on survival.

Evaluation: The text is in accordance with 21CFR, 201.50, Subpart B (April 1, 1998).

Evaluation: The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998).

SUMMARY AND EVALUATION:

Pantoprazole is a benzimidazole sulfoxide, which irreversibly inhibits gastric parietal cell H^+/K^+ -ATPase. At acid pH values, this compound rearranges to form a cationic sulfenamide which enters into covalent binding with SH-group-carrying enzymes, such as H^+/K^+ -ATPase. Pantoprazole is a racemic mixture composed of (+) and (-) enantiomers, which are approximately equipotent with regard to inhibition of H^+/K^+ -ATPase. The binding reaction to this enzyme, which is covalent in nature, effectively inhibits acid secretion until new enzyme is synthesized. [Since pantoprazole acts at the terminal step of the acid secretory pathway, agents, such as ATP, dibutyryl-cyclic AMP, histamine, and carbachol, that stimulate acid secretion by acting at various steps of this pathway, were shown to have little or no effect with in vitro studies using permeabilized rabbit fundic glands. In vivo studies with pantoprazole administered by the intravenous route to rats demonstrated inhibition of basal gastric acid secretion as well as secretion induced by 2-deoxy-d-glucose, bethanechol, pentagastrin. The sponsor speculated that the inhibitory effect of pantoprazole was predominantly on volume of secretion rather than acid concentration. Pantoprazole administered by the

intravenous route inhibited histamine or impromidine (H_2 receptor agonist)-stimulated gastric acid secretion in the Heidenhain pouch beagle dog. Pantoprazole administered by the intravenous route inhibited the formation of gastric mucosal lesions induced by aspirin in the modified Shay rat. Inhibition of gastric mucosal lesions paralleled inhibition of gastric acid secretion. Metabolites of pantoprazole appear to have little or no pharmacological activity as compared to the parent compound.

Pantoprazole (PROTONIX™ I.V.) is indicated for short term gastric acid suppression in gastroesophageal reflux disease patients who are unable to take oral medication. The duration of treatment will be ≤ 7 days. The therapeutic dose of pantoprazole is 40 mg/day or 0.8 mg/kg for a 50 kg individual.

The sponsor has submitted the preclinical pharmacology and toxicology studies in support of pantoprazole (PROTONIX™) enteric-coated tablets as follows: pharmacology; absorption, distribution, metabolism, and excretion studies in mice, rats, dogs, and monkeys; acute toxicity studies with pantoprazole in mice, rats, and dogs; acute toxicity studies with (+) and (-) enantiomers of pantoprazole in mice; acute toxicity studies with B8810-04 in mice and rats; four 4-week intravenous toxicity studies with pantoprazole in rats; a 4-week intravenous toxicity study with B8810-04 in rats; a 2-week toxicity study in beagle dogs using the intravenous and oral routes with special emphasis on toxic effects on the eyes and ears; a 30-day intravenous toxicity study in beagle dogs; a 4-week continuous intravenous infusion toxicity study with beagle dogs; 2-year carcinogenicity studies with pantoprazole in B6C3F1 mice, Sprague Dawley rats, and Fischer 344 rats; studies of tumor promoting potential in liver, thyroid, stomach, and forestomach in rats; reproductive toxicology studies that included oral Segment I fertility and reproductive performance studies in male and female rats, intravenous Segment II teratology studies in pregnant female rats and rabbits, and an oral Segment III perinatal and postnatal development study in rats; genotoxicity studies with pantoprazole that included a bacterial reverse mutation assay, chromosomal aberration assays with human lymphocytes (4 studies), a Chinese hamster ovary/HGPRT assay, an unscheduled DNA synthesis assay using primary rat hepatocytes, a AS52/GPT mammalian cell-forward gene mutation assay, a cell mutation assay at the thymidine kinase locus in mouse lymphoma L5178Y cells, a malignant transformation assay in C3H-M2 fibroblasts, two mouse micronucleus tests, a bone marrow chromosomal aberration assay in rats, an in vivo DNA binding assay and a ^{32}P -postlabeling experiment; genotoxicity studies with the thiol metabolite of pantoprazole that included a bacterial reverse mutation assay, two mouse micronucleus assays, and a malignant cell transformation assay in C3H-M2 fibroblasts; a bacterial reverse mutation assay with B8810-04; pulmonary toxicity studies with pantoprazole and its thiol metabolite in rats and beagle dogs; a 28-day electroretinographic study in cynomolgus monkeys; studies of antigenicity and sensitization that included a guinea pig maximization tests with pantoprazole and its thiol metabolite, an active systemic anaphylaxis test in guinea pigs, and a homologous passive cutaneous anaphylaxis test in guinea pigs; local tolerance studies that included local toxicity tests in rats after intramuscular administration, local toxicity tests in rabbits with pantoprazole and its lyophilisate after intravenous,

paravenous, and intra-arterial administrations, acute dermal irritation tests with pantoprazole and its thiol metabolite, and acute intravenous and perivenous irritancy tests with dogs; and assessment of *in vitro* effects on red blood cells that included hemolysis and membrane stability tests. For *in vivo* toxicology studies, dosages were expressed in terms of the free acid, except for acute toxicity studies, where dosages were expressed in terms of the sodium salt.

The absorption, distribution, metabolism, and excretion of pantoprazole were examined in mice, rats, dogs, and monkeys. Pharmacokinetic studies in mice, rats, dogs, and cynomolgus monkeys that received pantoprazole (radiolabeled in the benzimidazole ring or adjacent to the pyridyl ring for several studies) by the intravenous or oral route found that 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 mice, rats, dogs, and monkeys encompassed values observed in healthy human volunteers that received pantoprazole at a therapeutic dose of 40 mg/day (equivalent to 0.8 mg/kg for a 50 kg person). Plasma AUC values for unchanged drug following a single intravenous administration of pantoprazole were as follows: rats that received a dose of 5 mg/kg were observed with a value of _____ $\mu\text{g}\cdot\text{hr}/\text{mL}$, dogs that received doses of 10 to 40 mg/kg were observed with values of _____ $\mu\text{g}\cdot\text{hr}/\text{mL}$, and cynomolgus monkeys that received doses of 5 to 15 mg/kg were observed with values of _____ $\mu\text{g}\cdot\text{hr}/\text{mL}$. The mean plasma AUC value for unchanged drug in healthy human male volunteers, who received a therapeutic dose of pantoprazole at 40 mg/day by the intravenous route was _____ $\mu\text{g}\cdot\text{hr}/\text{mL}$. Plasma AUC values for the parent compound were found to represent a small fraction of the total radioactivity suggesting extensive metabolism. The half-lives of the parent compound in most species were generally <1 hr. The half-life of pantoprazole following intravenous administration to human volunteers was approximately 1 hr. Non-linear toxicokinetics of pantoprazole may be due to metabolism of pantoprazole. Pantoprazole [(±)-PAN] is a chiral sulfoxide. Following oral or intravenous administration of (+)-PAN to rats, there was significant chiral interconversion to form (-)-PAN; however, no interconversion was found following administration of (-)-PAN. Pantoprazole binding with rat and human serum protein exceeded 95%. Binding with dog serum protein was lower at 80-90%. Autoradiography studies with rats that received pantoprazole, with ^{14}C -label located at the C-2 position of the benzimidazole ring, by the intravenous route, found that radioactivity was widely distributed following administration and peak concentrations of radioactivity were generally found in all tissue at 1 hr after dosing. Plasma concentrations declined over time; however, radioactivity levels in whole blood remained relatively constant from 24 to 96 hr after dosing due to association of radiolabeled material with red blood cells. The liver and kidney appeared to be excretory organs. In autoradiography studies, using pantoprazole with ^{14}C -label adjacent to the pyridyl ring, results were similar; however, binding with erythrocytes was not evident due to loss of the radiolabel. This experiment indicated that the benzimidazole moiety and not the pyridyl ring of pantoprazole was responsible for binding to cellular component(s) of red blood cells.

Studies using pregnant female rat that received ^{14}C -pantoprazole indicated that drug or its metabolites crossed the placenta and fetal retention of radioactivity increased as the pregnancy progressed. Studies using lactating female rats that received ^{14}C -pantoprazole, found radioactivity in milk collected from suckling neonates. Proton pump inhibitors, such as pantoprazole, undergo extensive metabolism by cytochrome P450 as well as induce the activities of specific isozymes and inhibit the metabolism of other substrates (i.e., drugs). Using human liver microsomes fractions, it was found that pantoprazole was mainly metabolized by CYP2C19 and CYP3A4 isozymes of cytochrome P450, but very little metabolism was carried out by CYP2D6 isozyme. Other studies suggested that P450 isozymes, 2D6 and 2C9-10, also appeared to play roles in biotransformation. For female rats treated with pantoprazole, hepatic content of cytochrome P450, cytochrome b5, and NADPH-cytochrome C reductase were increased and induction of P450 isozyme activities was determined to be of the phenobarbital-type; although, it was 0.025 times as potent as phenobarbital on a molar basis. Pantoprazole acted as a specific inducer of isoforms, CYP2B1 and CYP2B2. No evidence of liver peroxisomal proliferation activity was evident. The thiol metabolite of pantoprazole had no effect on phase I (P450-dependent mixed-function oxidase) activities in rats; however, the thiol metabolite as well as pantoprazole significantly induced hepatic drug metabolizing enzyme activities which catalyze conjugation reactions (Phase II reactions: UDPGT- and glutathione S-transferase activities). The potency of pantoprazole with regard to phase II reactions was $\leq 50\%$ of phenobarbital on molar basis, while potency of the thiol was equivalent to phenobarbital. For female rats treated with pantoprazole at 200 mg/kg/day for 4-weeks, there were no significant changes in T_3 , T_4 and TSH levels even though UDPGT activity was induced. For mice, urinary and fecal excretion accounted for 30-34% and 38-50% of the elimination of drug-related compounds. For rats, about 60% and 40% of administered radioactivity were excreted in urine and feces, respectively. For dogs, 22-39% and 50-56% of the administered oral dose were excreted in urine and feces, respectively. For cynomolgus monkeys, the principal route of elimination was renal excretion. Following oral or intravenous administration of drug to human volunteers, urinary excretion accounted for $\leq 90\%$ of drug-related compounds, while fecal excretion accounted for $\leq 18\%$. For bile duct-cannulated rats, about 40-44% of the administered radioactivity was excreted in the bile. The total number of drug-related compounds detected in rats and dogs were 31 and >24 , respectively. Unchanged parent drug and the sulfone metabolite (SK&F 97167) were the major circulating drug-related compounds detected in plasma for rats and dogs. The thiol metabolite (SK&F 97165), associated with pulmonary toxicity was also detected in rat and dog plasma at low levels. The number of urinary radiometabolites detected in rats and dogs were 24 and 10-20, respectively, with each metabolite generally accounting for $<5\%$ of the administered dose. The primary routes of biotransformation for metabolites observed in urine for rats and dogs were hydroxylation of the benzimidazole ring and demethylation of either of the two methoxy groups on the pyridyl ring. Subsequent conjugation with sulfation or glucuronidation occurred. The number of metabolites detected was further increased by simultaneous oxidation or reduction of the sulfoxide group to either the sulfone or sulfide oxidation states. Feces collected from rats were found to contain no conjugated metabolites, as expected, and all metabolites had been reduced to the sulfide oxidation state. The main

identified metabolites in the feces were the desmethylhydroxylated sulfide, sulfide, and hydroxysulfide. Fecal elimination was the main route of excretion in dogs, and major components in fecal extracts were identified as the sulfide (SK&F 97166), hydroxysulfide, and desmethylsulfide. For rats, 18 metabolites were detected in the bile. Metabolites of pantoprazole undergo enterohepatic recycling. Four major metabolites of pantoprazole have been identified in human plasma. Three of these compounds designated as M1, M2, and M3 are sulfate conjugates of pantoprazole at the 4-position of the pyridine ring, which has been metabolically O-demethylated. M2 is a sulfoxide similarly to pantoprazole, whereas for M1 and M3, the sulfoxide group has been oxidized or reduced to the corresponding sulfone or sulfide, respectively. M2 is the predominant metabolite observed in the plasma. A minimum of 10 urinary radiometabolites were observed in humans, which accounted for 46-67% of the administered dose. Unchanged pantoprazole was not observed. Based upon metabolites observed in the urine, the major pathway of pantoprazole metabolism was p-O-desmethylation on the pyridine ring moiety followed by sulfation or glucuronidation. Both reduction to the sulfide and oxidation to the corresponding sulfone were also observed with and without subsequent conjugation. Two major metabolites were observed in fecal extracts. Metabolism of pantoprazole in healthy human male volunteers appears to occur through many of the same pathways observed in rats and dogs.

The acute toxicity of pantoprazole by the intravenous route was examined in NMRI mice, Sprague Dawley rats, and beagle dogs (dosages expressed in terms of the sodium salt). In mice that received pantoprazole by the intravenous route, the maximum nonlethal and minimal lethal doses were 350 and 400 mg/kg, respectively. Estimated intravenous LD₅₀ values in male and female mice were 399 and 395 mg/kg, respectively. In rats that received pantoprazole by the intravenous route, the maximum nonlethal doses in males and females were 200-250 and 200-260 mg/kg, respectively. The minimum lethal doses in male and female rats were 250-300 and 250-320 mg/kg, respectively. The estimated intravenous LD₅₀ values in male and female rats were 200-331 and 256-343 mg/kg, respectively. In beagle dogs following intravenous administration of pantoprazole, the maximum nonlethal and approximate minimum lethal doses were 150 and 300 mg/kg, respectively. Clinical signs in mice, rats, and dogs following oral or intravenous administration of pantoprazole were similar and included decreased activity and ataxia.

The acute toxicity of the (+) enantiomer of pantoprazole (B9010-007) was examined in mice at intravenous doses ranging from 170 to 450 mg/kg. Reduced activity, prostration and increased respiration rate were seen in all treated mice. Tremors and convulsions were also seen in some of the treated mice. The highest non-lethal dose was 220 mg/kg for mice of both sexes. The minimum lethal dose was 270 mg/kg (both sexes). The intravenous LD₅₀ values in male and female mice were 302 and 390 mg/kg, respectively, and were relatively similar to values found with the racemic mixture.

The acute toxicity of the (-) enantiomer of pantoprazole (B9010-026) was examined in mice at intravenous doses ranging from 170 to 370 mg/kg. Ataxia, loss of muscle tone and prostration were seen in all treated mice. The highest non-lethal I.V. doses were 170 mg/kg for males and 220 mg/kg for females. The minimum lethal I.V. doses were 220 mg/kg in males and 270 mg/kg in females. Intravenous LD₅₀ values in male and female mice were 244 and 220-270 mg/kg, respectively. The intravenous LD₅₀ value of the (-) enantiomer appears to be significantly lower than that observed for the (+) enantiomer or the racemate (estimated intravenous LD₅₀ values for pantoprazole in male and female mice were 399 and 395 mg/kg, respectively). This toxicity of the (-) enantiomer may be of concern, due to in vivo interconversion of the (+) enantiomer to the (-) enantiomer.

The compound, [redacted] is an impurity found in the lyophilized formulation of pantoprazole for intravenous injection. The acute intravenous toxicity of [redacted] was examined in mice and rats. Mice received [redacted] at doses ranging from 50 to 400 mg/kg. Rats received [redacted] at doses ranging from 40 to 114 mg/kg. The maximum nonlethal dose in female mice was 50 mg/kg; however, it was not determined for male mice. The minimum lethal doses in male and female mice were 50 and 65 mg/kg, respectively. LD₅₀ values for male and female mice were 119 and 167 mg/kg, respectively. For mice that received doses ≥ 50 mg/kg, clinical signs included prostration, loss of muscle tone, and increased respiratory rate. Deaths at doses of 50-400 mg/kg occurred within 8 min and were generally preceded by convulsions or muscle spasms. The maximum nonlethal dose in female rats was 52 mg/kg; however, it was not determined for male rats. The minimum lethal doses in male and female rats were 40 and 68 mg/kg, respectively. LD₅₀ values for male and female rats were 73 and 82 mg/kg, respectively. Clinical signs of toxicity for rats were similar to those observed for mice. Estimated intravenous LD₅₀ values for pantoprazole in male and female mice were 399 and 395 mg/kg, respectively. The estimated intravenous LD₅₀ values for pantoprazole in male and female rats were 200-331 and 256-343 mg/kg, respectively. The acute intravenous toxicity of [redacted] appears to be significantly greater than that of pantoprazole.

In a 4-week intravenous toxicity study, Sprague Dawley rats received pantoprazole at doses of 0, 1, 5, or 30 mg/kg/day. Selected rats from the control and 30 mg/kg/day groups were allowed a 30-day recovery period following the treatment period. The dose of 30 mg/kg/day 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 as they were not observed at the end of the 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 following the recovery period.

In a 4-week intravenous toxicity study, Sprague Dawley rats received pantoprazole at doses of 20 or 40 mg/kg/day. This study was flawed by the lack of a control group. Tachycardia and staggering gait were observed in males at 40 mg/kg/day. The stomach was the target organ of toxicity. At doses of 20 and 40 mg/kg/day, the borderline between the forestomach and gastric fundus showed hyperkeratosis. In the stomach, spreading of the foveolar zone was observed. An increase of the height of the mucosa in the gastric fundus appeared to exist. Bleeding, fibrosis and/or round cell infiltration were observed at the injection sites.

In a 4-week intravenous toxicity study, Wistar rats received pantoprazole at doses of 0, 10, 20, or 40 mg/kg/day. The lyophilized form of pantoprazole used in this study contained a low level of impurities. This batch was designated as an "unstressed batch". In stability tests with the lyophilized form of pantoprazole used for intravenous administration, the formation of a temperature-dependent impurity, _____, was detected. In order to extend the specification limits for lyophilized form of pantoprazole used for intravenous administration, the toxicity of batches with low (unstressed) and high (stressed) levels of impurities were compared in two parallel studies. In the present study with the "unstressed" batch of pantoprazole [Impurity _____ was present at _____ %], the dose of 20 mg/kg/day could be considered a tolerated dose. Changes at the injection site (i.e., tail blue, tail red, tail swollen) in the tail were more pronounced for pantoprazole treatment groups and occurred in a dose-related manner. Body weight gain was impaired by >10% for the male 40 mg/kg/day group. Gastrin levels were elevated for all treatment groups. The target organs of toxicity were the stomach and lungs. In the fundic part of the glandular stomach, a focal to multifocal eosinophilic discoloration of the cytoplasm of chief cells was observed at all dose levels. Histopathological changes in the stomach were most likely a pharmacological response to elevated gastrin levels. For the lung, an increased incidence of foreign body granuloma formation was found for the 40 mg/kg/day group; although, this was not a test article-specific effect. This study was flawed in that the sponsor did not examine all corresponding tissues from the low and mid dose groups where histopathological changes were identified in the high dose group.

In a 4-week intravenous toxicity study, Wistar rats received pantoprazole at doses of 0, 10, 20, or 40 mg/kg/day. The lyophilized form of pantoprazole used in this study contained a high level of impurities (Impurity _____ %, Total identified impurities = _____ %). This batch was designated as a "stressed batch". The dose of 20 mg/kg/day could be considered a tolerated dose. Mortality occurred for 1 female rat at a dose of 40 mg/kg/day. Localized tissue irritation at the injection site in the tail was increased in severity for pantoprazole-treatment groups. Gastrin levels were elevated for all treatment groups; although, there was no evidence of a dose response relationship. The stomach and liver were the target organs of toxicity. In the fundic part of the glandular stomach, a minimal focal to multifocal eosinophilic discoloration of the cytoplasm of chief cells was found in pantoprazole-treated animals at doses of 20 and 40 mg/kg/day. A dose-related increased incidence of centrilobular swelling of the liver was observed in pantoprazole treatment groups. This study was flawed in that the sponsor did not examine corresponding tissues from the low and mid dose groups

where histopathological changes were found in the high dose group. Study findings with "unstressed" and "stressed" lyophilized batches of pantoprazole generally consisted of well characterized findings this drug (i.e., changes in the stomach); although, mortality occurred for 1 (10%) female rat that received "stressed" pantoprazole at 40 mg/kg/day in contrast to no mortality for rats that received the "unstressed" form at this dose, and the "stressed" batch appeared to more potent with regard to centrilobular swelling.

In a 4-week intravenous toxicity study, Wistar rats received a temperature-dependent impurity identified in stability tests with pantoprazole, at doses of 0, 5, or 25 mg/kg/day. For comparison, rats received treatment with pantoprazole by the intravenous route at doses of 0 or 25 mg/kg/day for 4 weeks. The no effect dose for was 5 mg/kg/day. Body weight gain for male and female rats that received pantoprazole at 25 mg/kg/day was impaired by >10% during the treatment period; however weight gain was unaffected for rats received that received at 5 and 25 mg/kg/day. The target organs of toxicity for rats that received were the liver and stomach corpus. The target organ of toxicity for rats that received pantoprazole was the stomach corpus. Centrilobular hypertrophy of the liver was observed for rats that received at 25 mg/kg/day. Increased mucosal thickness of the stomach corpus was observed for rats that received either or pantoprazole at 25 mg/kg/day.

In a 6-month oral toxicity study, Sprague Dawley rats received pantoprazole at doses of 0, 0.8, 4, 16, and 320 mg/kg/day. For a complete summary and evaluation of this study, please refer to NDA 20,987. A hepatocellular adenoma was seen in 1/24 male rats treated with 320 mg/kg/day. A C-cell adenoma in thyroid was present in 1/24 females treated with 16 mg/kg/day at the end of the treatment period.

In a 12-month oral toxicity study, Sprague Dawley rats received pantoprazole at doses of 0, 5, 50, and 300 mg/kg/day. Additional rats were included in the 0 and 5 mg/kg/day groups for a 9-month recovery period following treatment. For a complete summary and evaluation of this study, please refer to NDA 20,987. One low dose treated male had a hepatocellular adenoma and another low dose male had a hepatocellular carcinoma. At the end of 9-month recovery period, a malignant neuroendocrine cell tumor (fundus) was observed for 1 of 11 female rats at 5 mg/kg/day. The presence of a gastric carcinoid at the end of recovery period for a female rat at 5 mg/kg/day suggests that cellular changes initiated during the treatment phase persisted through the recovery period. Gastric effects induced by pantoprazole at 5 mg/kg/day were not reversible.

In a 2-week intravenous/oral toxicity study, pantoprazole was administered to beagle dogs with special emphasis on measurement of possible visual and auditory disturbances. Compounds of the proton pump inhibitor class are suspected to cause visual and auditory disturbances. Dogs received pantoprazole by the intravenous route at doses of 0 and 60 mg/animal/day or the oral route at doses of 40 or 160 mg/animal/day for 2 weeks (15-18 days). The study was flawed in that there were no corresponding controls for groups that received pantoprazole by the oral route. Electroretinograms, visual evoked cortical potentials, and intraocular pressures for the right and left eyes on days 5 and 12 were unaffected by treatment. Auditory evoked potentials for the right and left ears on days 5 and 12 were unaffected by treatment. The target organs of toxicity were the stomach and the lungs. Parietal cell vacuolation and eosinophilic parietal cells were observed in the stomach for 1 male dog in 60 mg/day-IV group. Increased activity of lymph follicles in the gastric antrum was observed for 1 male dog in the 160 mg/day-oral group. Alveolar histiocytosis was observed in all three pantoprazole treatment groups. Alveolar emphysema was observed in the 40 mg/day-oral and 60 mg/day-IV groups.

In a 30-day intravenous toxicity study, beagle dogs received pantoprazole at doses of 0, 10, 20, or 40 mg/kg/day (30-min infusion, 4 mL/kg/day). A positive control group was also included, which received SK&F 95448-Z (40 mg/kg/day; compound with unknown structure that produces necrotizing vasculitis). The dose of 40 mg/kg/day could be considered a tolerated dose given that changes observed in the stomach, described below, were a result of the pharmacological action of the drug. Plasma gastrin levels were elevated in all pantoprazole treatment groups; although, a dose response relationship was not evident. Necrotizing arteritis was seen in one positive control treated dog; however, this finding was not seen in pantoprazole-treated dogs. The stomach was the target organ of toxicity. Parietal cell vacuolation was observed in all pantoprazole treatment groups as well as the positive control. Cytochrome P-450 content was slightly increased for male dogs that received pantoprazole at 40 mg/kg/day; although, no change was observed for female dogs. Pantoprazole at 40 mg/kg/day had no significant effects on hepatic ethylmorphine N-demethylase activity. Plasma C_{max} and AUC values for pantoprazole on days 1 and 30 increased in a manner proportional to ascending dose.

In a 4-week continuous intravenous toxicity study, beagle dogs received pantoprazole at doses of 0, 6, 18, and 36 mg/kg/day. Two dogs/sex from the control and 36 mg/kg/day groups entered an 8-week recovery period following the 4-week treatment period. The dose of 36 mg/kg/day appeared to be well tolerated. Serum gastrin levels were increased at weeks 1 and 4 for pantoprazole treatment groups; however, there was not a dose response relationship. There were no consistent treatment-related changes of triiodothyronine, thyroxine, or thyroid stimulating hormone. The stomach and lungs were the target organs of toxicity. For the stomach, an increased incidence of apoptosis of parietal cells was found for pantoprazole treatment groups. This histopathological change was attributed to a pharmacological alteration in the cell cycle of the parietal cell, the acid-producing cell of the gastric mucosa. For the lungs, subacute inflammation was observed for all pantoprazole treatment groups; however, there was no dose response relationship. Changes in stomach parietal cells were not evident following an 8-week recovery period. For the lung, subacute inflammation was still present following the recovery period.

The carcinogenetic potential of pantoprazole was assessed in two-year studies with B6C3F1 mice, Sprague Dawley rats, and Fischer 344 rats. The sponsor raised the possibility that pantoprazole might have tumor promoting potential. In response, the Division requested that the sponsor assess its tumor promoting potential in liver, thyroid, stomach, and forestomach in rats. Two studies were submitted by the sponsor, which assessed the tumor promotion potential of pantoprazole. In the first study, the tumor promoting activity of pantoprazole was assessed in the stomach and forestomach of Sprague Dawley rats in combination with a strong initiating carcinogen, N-methyl-N-nitroso-guanidine. In the second study, the tumor promoting activity of pantoprazole was assessed in the liver and thyroid gland of Sprague Dawley rats in combination with a strong initiating carcinogen, N-nitroso-N-methylurea.

In a 2-year carcinogenicity study, B6C3F₁ mice received pantoprazole by oral gavage at doses of 5, 25, and 150 mg/kg/day. Two additional groups were also included in the carcinogenicity study, one group was given vehicle (distilled water at pH 10.4) and the other group was used as an untreated cage control. At study termination, the survival rate for male mice at 150 mg/kg/day was reduced to 50% as compared to 84% for the cage control and 82% for the vehicle-control. Survival rate for female mice at 150 mg/kg/day was reduced to 62% as compared to 88% for the vehicle-control. There were no treatment-related effects on final body weights or food consumption. With regard to non-neoplastic histological findings, the target organs of toxicity were the stomach, liver, heart, gall bladder, and kidneys. For the stomach, a dose-dependent increase in the incidence of hyperplasia of the fundic region was found for both male and female mice. Dose-related increases in the incidence of focal and chain Grimelius Positive Cells (GPC) were found in male treatment groups. Submucosal growth was observed for male rats at 150 mg/kg/day. An increased incidence of focal, chain, and micronodule GPC were found for female mice at 150 mg/kg/day. For the liver, statistically significant increases in the incidence of Kupffer cell proliferation, patchy necrosis, fatty changes, and single cell necrosis were found for male and female mice at 150 mg/kg/day. Centrilobular necrosis was found for male mice at 25 and 150 mg/kg/day. An increased incidence of hepatocyte hyperplasia was observed for female mice at 150 mg/kg/day. For the heart, an increased incidence of distended chambers was found for male and female mice at 150 mg/kg/day. For the gall bladder, an increased incidence of distension was found for male mice at 150 mg/kg/day. For the kidney, an increased incidence of tubular dilation was found for male mice at 150 mg/kg/day. Additionally, 1 male mouse at 150 mg/kg/day was observed with osseous metaplasia in the kidney. For neoplastic findings, statistically significant increases in the incidence of hepatocellular adenomas ($p = 0.0257$) and carcinomas ($p = 0.0004$) were found for female mice at 150 mg/kg/day. The combined incidence of hepatocellular adenomas and carcinomas were significantly increased for female mice at 150 mg/kg/day. The combined incidence of liver-tumors (adenomas + carcinomas) in female mice that received pantoprazole at 150 mg/kg/day exceeded incidences reported in the sponsor's historical control data (mean = 7.6% with a range of 6-8.2%) and published literature (Haseman *et al.* *Journal of the National Cancer Institute* 75: 975-984, 1985, mean = 8.3% with a range of 0-20%; Maronpot *et al.*, *Arch. Toxicol. Suppl.* 10: 10-26, 1987). The mean time to liver tumor (adenomas and/or carcinomas) was not affected by the treatment. Thus, hepatocellular adenomas and carcinomas found in female mice at 150 mg/kg/day were induced by pantoprazole treatment.

The Carcinogenicity Assessment Committee reviewed the findings of the carcinogenicity study with pantoprazole in mice on September 7, 1994. The deliberations of the committee are briefly summarized here. There was consensus that the mouse study was performed at doses sufficiently high to provide an adequate challenge for carcinogenic potential (i.e., Maximum Tolerated Dose criteria were satisfied). The conduct of the mouse study was considered acceptable and valid data. The Carcinogenicity Assessment Committee concurred with the Division's assessment of a positive tumorigenic potential for pantoprazole.

In a 2-year carcinogenicity study, Sprague Dawley rats received pantoprazole by oral gavage at doses of 0, 0.5, 5, 50, and 200 mg/kg/day. At study termination, survival rates in female rats were comparable in the control and all treatment groups. However, the survival rate for male rats at 200 mg/kg/day was reduced to 4% as compared to 16% for male controls. It should be noted that survival rates were poor in all groups of male and female rats including the controls, and reached an unacceptable level of <50% at study termination. Less than 20 male rats/group were available at study termination for analysis. From day 526 to study termination, male rats in the control and all treatment groups lost body weight; although, food consumption was unaffected by treatment. No evidence of weight loss during this period was observed for female rats in control or treatment groups. These rats were specific pathogen-free prior to the start of treatment; however, no documentation was provided to show if rats were screened for pathogens during the treatment period. During this period, the mortality rate in male rats at 200 mg/kg/day exceeded the rate observed in controls. Decreased survival for male rats at 200 mg/kg/day can be attributed to pantoprazole treatment as well as possibly unknown pathogens. Final body weight for female rats at 200 mg/kg/day was 89% of the control. Toxicokinetic analysis revealed that plasma pantoprazole levels increased with ascending dose. The thiol metabolite was consistently observed in male and female rats at doses ≥ 50 mg/kg/day. With regard to non-neoplastic histological changes, the stomach, liver, thyroid gland, sternebra, kidneys, and testes were the target organs of toxicity. For the stomach at doses ≥ 0.5 mg/kg/day, there were increased incidences of fundic gland ectasia and eosinophilic chief cells in the fundus. At doses ≥ 5 mg/kg/day, there were increased incidences of hyperplasia of chromogranin positive cells in the fundus and increased height of the fundic mucosa. At doses ≥ 50 mg/kg/day, there was an increased incidence of hyperplasia of basal cells in the nonglandular stomach. For the liver at doses ≥ 50 mg/kg/day, there were increased incidences of centrilobular hepatocellular hyperplasia and eosinophilic cell focus. At doses ≥ 50 mg/kg/day for female rats, there was an increased incidence of basophilic cell focus. At a dose of 200 mg/kg/day, there was an increased incidence of hepatocellular necrosis. For the thyroid gland at doses ≥ 50 mg/kg/day, there was an increased incidence of follicular cell hypertrophy. The incidence of bilateral parathyroid hyperplasia was increased for male rats at doses ≥ 0.5 mg/kg/day and slightly for female rats at doses ≥ 50 mg/kg/day. For the sternebra of male rats at doses ≥ 5 mg/kg/day and female rats at doses ≥ 50 mg/kg/day, there was an increased incidence of fibrous osteodystrophy. For the kidneys of male rats at doses ≥ 5 mg/kg/day and female rats at doses ≥ 50 mg/kg/day, there was an increased incidence of mild to severe nephropathy.

For the testes of male rats at doses ≥ 50 mg/kg/day, there were increased incidences of interstitial cell hyperplasia and polyarteritis nodosa. At a dose of 200 mg/kg/day, the incidence of tubular degeneration for the testes of male rats was increased. For neoplastic histological findings, drug-related changes were evident in the stomach, liver, and thyroid gland. For the stomach, pantoprazole treatment produced benign + malignant neuroendocrine cell tumors (i.e., gastric enterochromaffin-like cell carcinoids) of the fundus in a dose-related manner for female rats at 0.5 to 200 mg/kg/day. For male rats, benign neuroendocrine cell tumors of the fundus were observed for 6 rats (8.6%) at 50 mg/kg/day (found during days 646-734) and 1 rat (1.4%) at 200 mg/kg/day (found on day 539). The low incidence of neuroendocrine cell tumor for male rats at 200 mg/kg/day was most likely due to the decreased survival rate for this group as well as the observation that these types of tumors tend to appear close to the end of 2-year study period. Benign squamous cell papillomas in the forestomach were observed for 2 female rats at 50 mg/kg/day and 7 male rats and 1 female rat at 200 mg/kg/day. Malignant squamous cell carcinomas in the forestomach were observed for 2 male rats at 50 mg/kg/day and 4 female rats at 200 mg/kg/day. The combined incidence of squamous cell papilloma and carcinoma was 2 male and 2 female rats at 50 mg/kg/day and 7 male and 5 female rats at 200 mg/kg/day. The combined incidences of squamous cell papilloma and carcinoma in male and female rats at 50 and 200 mg/kg/day were higher than the incidences in the sponsor's historical control data (mean = 0.36% with a range of 0-1.4%). A chief cell adenocarcinoma in the fundus was observed for 1 female rat at 200 mg/kg/day. Benign adenomatous polyps in the fundus were observed for 2 male rats and 1 female rat at 200 mg/kg/day. A malignant adenocarcinoma in the pyloric region was found for 1 male rat at 50 mg/kg/day. Although, incidences of these three tumors were not statistically significant by pairwise comparison with controls, nevertheless, these tumors were rare (McMartin *et al.* Toxicol. Pathol. 20: 212-225, 1992) and were drug-related. Further, it should be emphasized that there were no similar tumor findings for the control group. For the liver, there were dose-related increases in the incidence of hepatocellular adenomas and carcinomas in both male and female treatment groups. The incidences of hepatocellular adenomas and carcinomas in pantoprazole-treated rats (males: 21% and females: 36%) were higher than the sponsor's historical control data (males: range of 1.4-4.3% and females: 0.7% with a range of 0-1.4%). For the thyroid gland, there was an increased incidence of follicular cell adenoma in both male and female rats at 200 mg/kg/day. The incidences of follicular cell carcinoma and was increased in female rats at 200 mg/kg/day. The combined incidence of thyroid follicular cell adenoma + carcinoma in rats at 200 mg/kg/day (males: 11% and females: 9%) was higher than the incidence in the sponsor's historical control data (males: 2.1% with a range of 1.4-2.8% and females: 0.7% with a range of 0-1.4%). Malignant neuroendocrine cell tumors of unknown origin were observed in the liver for 1 male rat in each of the 5, 50, and 200 mg/kg/day groups, which indicated the occurrence of tumor metastases (for #M4718 at 5 mg/kg/day and #M4997 at 200 mg/kg/day, no primary tumors were evident). Additionally, neuroendocrine cell tumors of unknown origin were observed in lymph node for 1 of 70 males at 50 mg/kg/day and 1 of 70 females at 200 mg/kg/day) and in several organs (i.e., abdomen, lung, liver, lymph node, and pancreas) for 1 of 70 females at 200 mg/kg/day, which, further, indicate the occurrence of tumor metastases. Pantoprazole was considered to be positive with regard to tumorigenic potential given the tumor findings in the stomach, liver, thyroid gland, and kidneys in rats of both sexes and their incidences.

The Carcinogenicity Assessment Committee reviewed the findings of the carcinogenicity study with pantoprazole in rats on September 7, 1994. The deliberations of the committee are briefly summarized here. There was consensus that the rat study was performed at doses sufficiently high to provide an adequate challenge for carcinogenic potential (i.e., Maximum Tolerated Dose criteria were satisfied). There was concern regarding the validity of the study due to body weight losses, escalating mortality in all groups of male rats including controls, low survival in all groups including controls at study termination, and lack of evidence for health and pathogen screens over the course of the study. However, analysis of survival curves indicated excellent survival at 18 months (61-76% for males and 74-86% for females) and at 21 months (36-50% in males and 51-61% for females). This suggested that survival was sufficient to allow drug exposure for a sufficient portion of the animal's lifetime to be an acceptable test of carcinogenic potential. The presence of tumors and target organs of toxicity expected for this drug class also supported the validity of this study. The Carcinogenicity Assessment Committee concurred with the Division's assessment of a positive carcinogenic potential for pantoprazole.

In the 2-year carcinogenicity study with pantoprazole in Sprague Dawley rats, malignant neuroendocrine cell tumors were observed in the liver for 1 male rat in each of the 5 (animal # M4718), 50 (animal # M4883) and 200 (animal # M4997) mg/kg/day dose groups. Additionally, neuroendocrine cell tumors were observed in lymph node (animal # M4870 at 50 mg/kg/day and # F5070 at 200 mg/kg/day) and in several organs (i.e., abdomen, lung, liver, lymph node, and pancreas) of 1 female rat (# F5108) at 200 mg/kg/day. The sites of origin for these tumors were not identified, which was suggestive of metastasis. The sponsor used selective staining of tissue slides in an attempt to identify the origins of these tumors. The liver metastases of rats #M4718 and #M4997 showed marked insulin expression and a partially positive Grimelius reaction suggesting the origin of these tumors was the pancreas (i.e., islet cell carcinoma). The liver metastasis of rat # M4883 was most likely an anaplastic sarcoma as the Grimelius silver stain and chromogranin stain were negative, and the neuroendocrine tumor classification could be excluded. Tumors rat # F5108 gave positive reactions with chromogranin and Grimelius silver stains, confirming the original diagnosis of neuroendocrine tumors in the stomach. The tumor of rat # M4870 reacted strongly with a monoclonal antibody against lipase and was diagnosed to be acinar cell carcinoma of pancreas. Results of immunohistological staining with the tumor from rat # F5070 were not conclusive. It should be noted that the original histopathology reports for rat # M4178, # M4997 and # M4870 submitted with carcinogenicity study contained no data regarding carcinomas in the pancreas.

There were several neoplastic findings from the carcinogenicity study with pantoprazole in rats that differ significantly from carcinogenicity studies with other proton pump inhibitors (i.e., omeprazole and lansoprazole) in rats. This information was discussed in the Carcinogenicity Assessment Committee meeting on September 7, 1994. For the stomach, neuroendocrine cell tumors (benign + malignant) have been observed in the fundus with all three agents. These tumors are thought to result from a hypergastrinemia produced by the pharmacological action of these agents; however, no

elevation of serum gastrin levels were demonstrated in a 30-day study with pantoprazole doses of 0.5 or 1 mg/kg/day or in the 6-month toxicity study at a pantoprazole dose of 0.8 mg/kg/day, yet a malignant neuroendocrine cell tumor was observed at 0.5 mg/kg/day in the carcinogenicity study. Additional neoplastic changes were observed in the stomach from pantoprazole-treated rats that have not been found with omeprazole or lansoprazole. These changes included: squamous cell carcinomas and papillomas in the forestomach; and rare tumors observed in the gastric glandular mucosa including chief cell adenocarcinoma in the fundus of one female, adenomatous polyps in the fundus of two males and one female, and adenocarcinoma in the pyloric region in one male. Additionally, neuroendocrine cell tumors were found in the liver of one animal at each pantoprazole dose level without identification of primary site (i.e., suggesting metastasis). Pantoprazole produced hepatocellular adenomas and carcinomas in rats. The sponsor has contended that pantoprazole is like phenobarbital and induces cytochrome P450 microsomal enzymes in rats, and concluded liver tumors were related to the promoter activity of the drug. Electron microscopic examination of livers from pantoprazole-treated rats has confirmed proliferation of the smooth endoplasmic reticulum; although, this drug is a very weak hepatic enzyme inducer and possesses only 0.025 times the potency of phenobarbital on a molar basis. Proton pump inhibitors, pantoprazole, omeprazole, and lansoprazole, are all weak hepatic enzyme inducer; however, in two-year carcinogenicity studies, only pantoprazole produced hepatocellular adenomas and carcinomas in the rat, which were statistically significant for both sexes. Thus, liver tumors observed in pantoprazole-treated rats cannot be explained solely on the basis of hepatic microsomal enzyme induction. Pantoprazole produced significant increases in the incidences of thyroid follicular cell adenomas and carcinomas in both male and female rats, which were not observed in 2-year carcinogenicity studies with omeprazole and lansoprazole. The sponsor has contended that thyroid tumors were generated in response to an imbalance of thyroid metabolism (i.e., Thyroid stimulating hormone-driven). TSH-driven thyroid follicular hypertrophy and hyperplasia can result from either direct inhibition of thyroid peroxidase (which incorporate iodine into T₄ and T₃) or indirectly through metabolism (i.e., glucuronide conjugation) and/or excretion (i.e., biliary), and receptor-mediated effects at hypothalamic and pituitary levels. In a 4-week study of thyroid function with Sprague Dawley rats, pantoprazole at 500 mg/kg/day decreased T₃ levels by 29-40% of the control and increased TSH levels by 2- to 3-fold; however, at 200 mg/kg/day, the highest dose used in the carcinogenicity study, there were no changes in T₃ or TSH levels. In a 2-week study with Sprague Dawley rats, pantoprazole at 200 mg/kg/day, the highest dose used in the carcinogenicity study with Sprague Dawley rats, had no effect on thyroid peroxidase activity and subsequent biosynthesis of thyroid hormones; although, uptake of iodine was enhanced as compared to the control following TSH stimulation. Following treatment of Sprague Dawley rats with either pantoprazole, lansoprazole, or omeprazole at doses of 5, 50, or 300 mg/kg/day for 1 week, significant induction of hepatic UDP-glucuronyl transferase (UDPGT) activity was observed with all three agents; however, the induction of UDPGT found with pantoprazole was smaller than that observed with either omeprazole or lansoprazole. Biliary excretion of [¹²⁵I]thyroxine (T₄) was significantly increased by the treatment of rats with all three agents; however, the increased biliary excretion of radiolabeled T₄ found with pantoprazole was much smaller than that observed with omeprazole or lansoprazole.

Thus, the effects of pantoprazole on induction of hepatic UDPGT activity and thyroid hormone metabolism were smaller than those observed for omeprazole or lansoprazole; however, in 2-year carcinogenicity studies, thyroid tumor were only been observed with pantoprazole. Thus, thyroid tumor observed in pantoprazole-treated rats cannot be explained by an imbalance of thyroid hormone metabolism (i.e., TSH-driven). In the 6-month oral toxicity study with Sprague Dawley rats, a hepatocellular adenoma was observed at 320 mg/kg/day. In the 12-month oral toxicity study with Sprague Dawley rats, a malignant neuroendocrine cell tumor was observed in gastric fundus at 5 mg/kg/day following a 9-month drug-free recovery period. Both in vitro and in vivo genotoxicity studies, described below, have shown that pantoprazole possesses mutagenic and clastogenic activity. These data demonstrate that pantoprazole possesses a carcinogenetic potential.

In a two-year carcinogenicity study, Fischer 344 rats received pantoprazole by oral gavage at doses of 5, 15, and 50 mg/kg/day. Two additional groups were also included in the carcinogenicity study, one group was given vehicle (distilled water pH 10.4) and the other group was used as an untreated cage control. No dose range finding studies were performed in order to select doses for this study with Fischer 344 rats. The sponsor contended that the high dose of 200 mg/kg/day, used in the carcinogenicity study with pantoprazole in Sprague Dawley rats, exceeded the maximum tolerated dose. Based upon these results with Sprague Dawley rats, the sponsor selected doses of 5, 15, and 50 mg/kg/day for the carcinogenicity study with pantoprazole in Fischer rats. However, as noted above, dose selection for the carcinogenicity study with pantoprazole in Sprague Dawley rats was judged to be adequate. Furthermore, it is not scientifically valid to assess the MTD in one strain of rat and conduct carcinogenicity study in another strain of rat. In a 90-day dose range finding study with the thiol metabolite of pantoprazole (B8401-026/SK&F 97165) in Fischer rats, the sponsor included a group that received pantoprazole at 200 mg/kg/day as a comparator. For Fischer rats that received pantoprazole at 200 mg/kg/day, there was no mortality or effects on body weight gain. Further, observed histopathological findings were of a minor nature and would not be expected to have any impact on survival. Thus, dose selection for the 2-year carcinogenicity study in Fischer rats was not appropriate. Treatment had no significant effect on mortality rates, final body weights, or food consumption. With regard to non-neoplastic findings, the target organs of toxicity were the stomach, liver, kidney, and adrenal glands. For the forestomach, there was a dose-related increase in the incidence of hyperplasia of the squamous epithelium in both male and female rats. For the fundus, there were increased incidences of eosinophilic chief cell hyperplasia, glandular ectasia, and basal fibrosis in both male and female rats; although, the incidences were not dose-related. There was an increased incidence of Grimelius positive cells focal hyperplasia and chain in the fundus for both male and female rats; although, dose response relationships were not evident. The incidence of micronodules of Grimelius positive cells was increased for both male and female rats at 15 and 50 mg/kg/day. The incidence of mucosal hyperplasia of antrum was increased for male and female rats at 15 and 50 mg/kg/day.

For the liver, the incidence of pigment deposits was increased for male rats at 50 mg/kg/day and the incidence of spongiosis was increased in male rats at 15 and 50 mg/kg/day. The incidence of centrilobular hepatocellular hypertrophy was increased for all male and female treatment groups. For the kidney, a dose-related occurrence of interstitial nephritis was observed in male treatment groups; although, the overall incidence was low. Chronic progressive nephropathy was observed in all control and treatment group; although, the severity was increased in male rats at 50 mg/kg/day. For the adrenal glands, there was an increased incidence of pigment deposit for male rats at 15 and 50 mg/kg/day. For neoplastic findings, the incidence of benign + malignant neuroendocrine cell tumors (i.e., gastric carcinoids) was increased for male rats at 15 and 50 mg/kg/day and female rats at 5, 15, and 50 mg/kg/day. The highest tested dose of 50 mg/kg/day in this study was not the MTD. In spite of this major deficiency, pantoprazole treatment induced neuroendocrine cell tumors (benign + malignant) in male rats at 15 and 50 mg/kg/day and in female rats at 5, 15, and 50 mg/kg/day. This study is not very informative, due to major flaws in dose selection, however, it confirms some findings of the carcinogenicity study in Sprague Dawley rats.

The tumor promoting activity of pantoprazole was assessed in the stomach and forestomach of Sprague Dawley rats. This mechanistic study was intended to evaluate the potential tumor promoting activity of pantoprazole in combination with a strong initiating carcinogen, N-methyl-N-nitroso-guanidine (MNNG). For a complete summary and evaluation of this study, please refer to NDA 20,987. Results were inconclusive regarding the tumor promotion potential of pantoprazole in the stomach and forestomach.

The tumor promoting activity of pantoprazole was assessed in the liver and thyroid gland of Sprague Dawley rats. This mechanistic study was intended to evaluate the potential tumor promoting activity of pantoprazole in combination with a strong initiating carcinogen, N-nitroso-N-methylurea (NMU). The study protocol was based upon the experimental protocol described by Diwan et al. (Journal of the National Cancer Institute 75: 1099-1105, 1985). For a complete summary and evaluation of this study, please refer to NDA 20,987. Results were inconclusive regarding the tumor promotion potential of pantoprazole in the liver and thyroid gland.

In an oral Segment I fertility and reproductive performance study, male Sprague Dawley rats received pantoprazole by gavage at doses of 0, 5, 50, and 500 mg/kg/day for 70 days prior to mating with untreated female rats. Pantoprazole at oral doses ≤ 500 mg/kg/day had no effect on fertility and reproductive performance in male rats.

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

In an intravenous Segment II teratology study, pregnant female Sprague Dawley rats received pantoprazole at doses of 0, 1, 4, or 20 mg/kg/day from days 6 to 15 of gestation. Pantoprazole at intravenous doses ≤ 20 mg/kg/day had no teratogenic effects in rats.

In an intravenous Segment II teratology study, pregnant female rabbits received pantoprazole at doses of 0, 1.5, 5, and 15 mg/kg/day from days 6 to 18 of gestation. Pantoprazole at intravenous doses ≤ 15 mg/kg/day was not teratogenic in rabbits.

In an oral Segment III perinatal and postnatal development study, pregnant female Sprague Dawley rats received pantoprazole by gavage at doses of 0, 1, 3 and 30 mg/kg/day from day 15 of gestation to day 21 after parturition. Pantoprazole at doses ≤ 30 mg/kg/day had no significant effects on perinatal and postnatal development in rats.

The genotoxic potential of pantoprazole was assessed with a number of in vitro and in vivo studies. 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 hepatic liver DNA. In four separate tests, chromosomal aberration assays using human lymphocytes with pantoprazole produced positive responses. In the CHO/HGRPT forward mutation assay, pantoprazole produced a positive response in 2 of 3 tests. In the mouse micronucleus test, doses of 177.5 and 710 mg/kg produced a positive response at the 24 hr sampling time. In a second mouse micronucleus test, doses ≤ 710 mg/kg at sampling times of 24 or 36 hr produced a negative response. In a covalent binding assay with rat liver DNA, pantoprazole produced a positive response. The covalent binding index was 1.6 for rats that received a 14-day pretreatment with 200 mg/kg/day pantoprazole followed by a single treatment with radiolabeled pantoprazole as compared to 0.70 for rats that received a 14-day pretreatment with vehicle followed by a single treatment with pantoprazole. This study clearly indicated that pantoprazole radioactivity could bind to rat liver DNA and pretreatment with pantoprazole for 14 days increased the covalent binding index by 2.3-fold. A ^{32}P -postlabeling experiment was performed with hepatic DNA obtained from female Sprague Dawley rats treated with pantoprazole by the oral route at a dose of 200 mg/kg/day for 4 weeks. DNA damage assessed by ^{32}P -postlabeling suggested that pantoprazole treatment led to the formation of a unique DNA adduct not observed in control samples. An "extra spot" was observed with pantoprazole samples in three different chromatography systems that was not found in control samples. These results suggested that pantoprazole or one of its metabolites directly interacts with DNA to form an adduct. Quantitation of DNA adducts provided by the sponsor was unclear;

however, analysis of chromatography patterns following nuclease P1 enhancement and descriptive narrative of results suggest that pantoprazole treatment led to the formation of a unique adduct. No such results were obtained with omeprazole (200 or 600 mg/kg/day) or lansoprazole (200 or 1200 mg/kg/day). Pantoprazole was negative in the in vitro bacterial reverse mutation assay, the unscheduled DNA synthesis assay with rat hepatocytes, AS52/GPT mammalian cell-forward gene mutation assay, thymidine kinase mutation test with mouse lymphoma L5178Y cells, malignant transformation assay with C3H-Mouse M2-fibroblasts, and SHE cell transformation assay. Pantoprazole was negative in vivo with the bone marrow chromosomal aberration test using rats. Genotoxicity studies indicate that pantoprazole can produce chromosomal aberrations with human lymphocytes, induce forward mutations at the HGPRT locus in Chinese hamster ovary cells, bind with rat liver DNA, and form adduct(s) with rat liver DNA. Pantoprazole possesses mutagenic and clastogenic activity.

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

The genotoxic potential of an impurity found in the lyophilized formulation of pantoprazole for intravenous injection, was assessed in vitro using the bacterial reverse mutation assay. possessed no genotoxic potential in bacterial reverse mutation assays using Salmonella typhimurium strains, TA1535, TA1537, TA98, and TA98, and Escherichia coli strains, WP2 and WP2uvrA, in the presence or absence of metabolic activation.

The sponsor has conducted a series of special toxicity studies to assess the effects of pantoprazole with regard to pulmonary toxicity, the eye, antigenicity and sensitization, local tolerance, and red blood cell hemolysis.

In early toxicity studies with pantoprazole in dogs, the development of a potentially fatal pulmonary toxicity was observed. To assess the potential pulmonary toxicity of pantoprazole, the sponsor conducted a number of studies with rats and dogs. Dogs appeared to be highly sensitive to pantoprazole-induced pulmonary toxicity, whereas rats were not. In a dose range finding toxicity study, beagle dogs received drug at intravenous doses of 0, 7.5, 15, 30, and 50 mg/kg/day for 5 days. At 50 mg/kg/day, death of one dog and moribund sacrifice of two other were attributed to pulmonary toxicity (i.e., fluid effusion into the pulmonary alveoli). Histopathological analysis of the lung for dogs at 50 mg/kg/day revealed areas of alveolar hemorrhage, eosinophilic material in alveoli (i.e., protein), and neutrophils in the alveoli. Areas of foamy alveolar macrophages were evident at doses ≥ 15 mg/kg/day. The no effect dose for

pantoprazole-induced pulmonary toxicity in dogs appeared to be 7.5 mg/kg/day. In another study, electron microscopy studies revealed evidence of necrosis of a small proportion of alveolar capillary endothelial cells, in dogs treated with pantoprazole for 5 days by the oral route at 100 mg/kg/day or by the intravenous route at 50 mg/kg/day, which was considered indicative of vascular leakage with fluid effusion into the alveoli. The toxicokinetic relationship between pulmonary toxicity and systemic exposure to the thiol metabolite of pantoprazole (B8401-026/SK&F 97165) was examined in beagle dogs that received either pantoprazole at intravenous 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 intravenous 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 found with pantoprazole at 50/40 mg/kg/day and the thiol metabolite at 5 and 15 mg/kg/day. Study parameters indicate that the same processes were occurring following administration of either pantoprazole or its thiol metabolite and that a dose-responsive relationship existed with both compounds. Systemic exposure to the thiol metabolite was $>700 \mu\text{g}\cdot\text{min}/\text{mL}$ in all dogs that had evidence of alveolar effusion. These findings seem to support the concept that pantoprazole-induced pulmonary toxicity might be associated with the thiol metabolite (B8401-026/SK&F 97165). The sponsor's analytical methodology to identify and quantify the thiol metabolite is highly questionable at the time of this review. It should be noted that the thiol metabolite appears to be highly reactive and most likely binds rapidly with cellular components.

In a 4-week intravenous toxicity study, cynomolgus monkeys received at doses of 0, 5, or 15 mg/kg/day. The no effect dose was 15 mg/kg/day. There was no target organ of toxicity. Electrocardiograph and blood pressure measurements revealed no biologically significant treatment-related changes. Ophthalmic and electroretinographic examinations revealed no biologically significant treatment-related changes.

Pantoprazole and its thiol metabolite (B8410-026) were assessed for antigenic and sensitization properties using well characterized models. Pantoprazole was negative in the guinea pig maximization test and in both the active systemic anaphylaxis and passive cutaneous anaphylaxis tests with guinea pigs. No delayed hypersensitivity reaction was observed in guinea pigs treated with the thiol metabolite of pantoprazole (B 8401-026).

Several local tolerance studies were performed with pantoprazole in rats, rabbits, and dogs and the thiol metabolite in rabbits. No differences in incidences or severity of necrosis or local signs of intolerance were found following intramuscular injection of either the placebo or pantoprazole to rats. No signs of local intolerance were observed with rabbits that received a single intravenous injection of a 0.4% pantoprazole solution; however, more extensive local reactions (i.e., discoloration, swelling, and scabs at the injection site) were observed with a 6% solution. Microscopic evaluation found hemorrhagic necrotizing tissue changes in the area around the central ear artery and clot formation (i.e., thrombus in organization or thrombotic residue) within the artery itself. These changes are presumed to occur due to occlusive vascular processes,

which may have caused by the pH of solution at 9 to 11. The sponsor stated that the maximum therapeutic concentration for parenteral use should be 2.56%. A single intravenous, paravenous, or intraarterial injection of 0.4% pantoprazole (free acid) into the ear did not produce local irritation in rabbits (two studies). Pantoprazole and its thiol metabolite (B8401-026) had a low potential of 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 to 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 3×10^{-4} M reduced the relative hypotonic hemolysis of dog and rat erythrocytes by 15-20% and human erythrocytes by 30%.

In humans, pantoprazole will be administered by the intravenous route for periods ≤ 7 days. The sponsor has conducted sufficient preclinical toxicology studies. In 4-week intravenous toxicity studies with pantoprazole, the target organ of toxicity for both Wistar rats and beagle dogs was the stomach. Finding in the stomach for rats consisted of a focal to multifocal eosinophilic discoloration of the cytoplasm of chief cells and for dogs consisted of parietal cell vacuolation. Histopathological changes observed in the stomach for both rats and dogs may possibly be related to increased circulating levels of gastrin produced by the pharmacological action of the pantoprazole.

Both in vitro and in vivo genotoxicity tests suggest that pantoprazole can bind with DNA and possesses mutagenic and clastogenic activity. Further, pantoprazole in carcinogenicity studies with B6C3F1 mice, Sprague Dawley rats, and Fischer 344 rats was found to have a positive tumorigenic potential. As discussed earlier, tumor findings with pantoprazole in the carcinogenicity study with Sprague Dawley rats differ significantly from findings with omeprazole and lansoprazole. For the stomach, neuroendocrine cell tumors (benign + malignant) have been observed in the fundus with all three drugs. These tumors are thought to result from a hypergastrinemia produced by the pharmacological action of these agents; although, no elevation of gastrin levels was demonstrated with pantoprazole at a dose level of 0.5 mg/kg/day, yet a malignant neuroendocrine tumor was observed. There were additional neoplastic changes observed in the stomach from pantoprazole-treated rats that have not been found with omeprazole or lansoprazole. These changes included squamous cell carcinomas and papillomas in the forestomach, a chief cell adenocarcinoma in the fundus, adenomatous polyps in the fundus, and an adenocarcinoma in the pyloric region. Neuroendocrine cell tumors were found in the liver, lymph nodes, and multiple organs, which indicated the occurrence of tumor metastases. Pantoprazole produced hepatocellular adenomas and carcinomas in rats, which cannot be explained solely on the basis of hepatic microsomal enzyme induction. Pantoprazole produced significant increases in the incidences of thyroid follicular cell adenomas and carcinomas, which were not observed in 2-year carcinogenicity studies with omeprazole and lansoprazole, and cannot be explained by an imbalance of thyroid hormone metabolism. In the 6-month oral toxicity study with

JAN 12 2000

MEMORANDUM

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

DATE: January 12, 2000

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

SUBJECT: NDA 20,988 (Pantoprazole Sodium for Injection) -
Amendment Dated August 31, 1999 -
Sponsor's Revised Draft Labeling.

TO: NDA 20,988

In the approvable letter dated July 20, 1999, the sponsor was provided labeling and asked to submit the final printed labeling identical in content to the supplied marked-up copy. Sponsor in their response dated August 31, 1999, submitted a revised draft labeling with several changes. The portions of the labeling that relate to preclinical data are similar to a large extent to the labeling of NDA 20,987 (PROTONIX Delayed-Release Tablets). To avoid duplication, portions of sponsor's version are reproduced below, followed by the Agency's current version faxed (1/11/00) to sponsor in the context of NDA 20,987 or a revised version. The specific portions are: I. Enterochromaffin-Like (ECL) Cell Effects under subsection pharmacodynamics of CLINICAL PHARMACOLOGY Section, II. Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of PRECAUTIONS section and III. OVERDOSAGE section.

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Draft Labeling

MEMORANDUM

(Review)

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

DATE: June 25, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

SUBJECT: NDA 20,987 (PROTONIX™-Pantoprazole Sodium Tablets) -
Rat Carcinogenicity Studies - Consultation from
Contracted Pathologists []
[]- Labeling Changes

TO: NDA 20,987

Because of the sponsor's proposed changes in the diagnoses of tumors of certain animals in the Sprague-Dawley rat carcinogenicity study and sponsor's expression of doubt about the accuracy of the diagnoses of granulocytic leukemia in three animals of the Fischer rat carcinogenicity study, the Carcinogenicity Assessment Committee asked the sponsor to provide the relevant histopathology slides and the tissue blocks for evaluation by [] pathologists. Pathologists of [] provided the results of their evaluation via a faxed memorandum dated June 24, 1999. At this point of time, the details of the materials provided by the sponsor are not known. The particulars of specific identification of the animals, the original diagnoses by the testing laboratory, the present sponsor's (Wyeth-Ayerst) diagnoses and the [] diagnoses are provided below.

Sprague-Dawley Rat Study

Animal # & Sex	Dose mg/kg/day	Original Finding by SmithKline Beecham	Present Sponsor's (Wyeth-Ayerst) Changed Diagnoses	Sponsored Pathologists Diagnoses
4718 (male)	5	Metastasis of NE- cell tumor in liver with no primary site	Pancreatic Islet cell carcinoma	Islet cell carcinoma, beta cell
4997 (male)	200	"	"	"
4883 (male)	50	"	Anaplastic sarcoma	Sarcoma, nos
5001 (male)	200	Adenomatous polyp- stomach	Adenomatous polyp, stomach	Adenomatous polyp, stomach
5055 (male)	200	"	"	"
5122 (female)	200	"	"	"
5108 (female)	200	NE-cell tumor- stomach & Metastases (lung, liver, duodenum, mesenteric lymph node & pancreas)	NE-cell tumor- stomach & metastases	Neuroendocrine cell tumor, malignant, Stomach with metastases to other organs. Adenomatous polyp-stomach
4908 (male)	50	Adenocarcinoma of stomach (pyloric region)	Adenocarcinoma- duodenum	Adenocarcinoma- duodenum
5070 (female)	200	NE-cell tumor- stomach & Lymph node metastasis	Pancreatic acinar cell carcinoma	Adenocarcinoma- stomach. Lymph node metastasis
5100 (female)	200	Chief cell adenocarcinoma- stomach NE-cell tumors- stomach	NE-cell tumors with areas of chief cell like differentiation or Chief cell adenocarcinoma with features of neuroendocrine cell differentiation	Mixed tumor- malignant NE-cell tumor- stomach & Adenocarcinoma- stomach

Fischer Rat Study

Animal # & Sex	Dose mg/kg/day	Original Finding by Byk-Gulden	Sponsor's (Wyeth- Ayerst) Changed Diagnosis	NCTR Diagnosis
83 (male)	15	Granulocytic Leukemia	Mononuclear cell leukemia/large granular lymphocyte leukemia	Mononuclear cell leukemia
41 (male)	50	"	"	"
410 (male)	50	"	"	"

While the memorandum of the [] (sponsored) indicates that their evaluation of the material, particularly of animal #5100 (Sprague-Dawley) is still ongoing, certain conclusions can be drawn based on their assessment thus far. The Fischer rat study had findings of granulocytic leukemia in 3 rats. This is a rare tumor for this strain of rats. The changed diagnoses of these tumors to mononuclear cell leukemia alleviates the concern. This study was, however, considered inadequate and inappropriate by the CAC. In the Sprague-Dawley rat study which was considered adequate and valid by the CAC, there were several tumor findings some of which are rare. The examination of the slides by [] sponsored pathologists confirmed that treatment with pantoprazole produced rare tumors. While the original diagnoses of pyloric adenocarcinoma is changed to duodenal adenocarcinoma, it is still a rare tumor for this strain of rat. The examination by [] sponsored pathologists, changed the diagnosis of chief cell adenocarcinoma to adenocarcinoma of the stomach (animal #5100-female). This coupled with the new finding of incidence of adenocarcinoma of the stomach in another female rat (#5070) gave an incidence of about 2.9%. Incidence of adenocarcinoma of the stomach in female rats of this strain is also extremely rare. The examination by [] sponsored pathologists also disclosed additional incidence of fundic adenomatous polyps of the stomach in another female rat (#5108). Thus treatment with pantoprazole produced benign and malignant neuroendocrine cell tumors of glandular stomach (ECL cell carcinoid), adenomatous polyps of the glandular stomach, adenocarcinoma of the glandular stomach, adenocarcinoma of the duodenum and squamous cell papilloma and carcinoma of the forestomach and increased the incidence of hepatocellular adenoma and carcinoma and thyroid follicular cell adenoma and carcinoma in Sprague-Dawley rats.

The "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the "PRECAUTIONS" section is changed to reflect the outcome of the histopathology examination by the _____ sponsored pathologists. The changed labeling is reproduced below.

ISI

6/28/99

Jasti B. Choudary, B.V.Sc., Ph.D.

ATTACHMENT: Fax Memorandum Dated June 24, 1999 from
Pathology Associates International

CC:

NDA

HFD-180

HFD-181/CSO/Ms. Walsh

HFD-180/Dr. Choudary

HFD-180/Dr. Robison

HFD-180/Dr. Gallo-Torres

HFD-180/Dr. Talarico

HFD-024/Dr. DeGeorge

HFD-024/Ms. Seifried

JBC/hw/6/28/99

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MEMORANDUM

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

DATE: June 3, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

SUBJECT: NDA 20,988 (PROTONIX™ I.V./Sterile
Pantoprazole Sodium) - Labeling -
Preclinical Portions.

TO: NDA 20,988

This is a follow-up to Dr. Robison's Pharmacology Review of NDA 20,988 dated April 30, 1999. The following represents the recommended version of portions of the sponsor's proposed labeling which are based on preclinical pharmacology and toxicology data. The corresponding portions in the sponsor's version should be deleted and replaced by the present Pharmacology version.

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Proposed Labeling

