**Animals:** Female New Zealand White Rabbit.

**Drug Batch No.:** 013927

**Methods:** Rabbits (3/group) were given a single I.V., paravenous (P.V.), or I.A. injection of 0.4% pantoprazole (free acid) in the ear. The volumes of injections were 1, 0.5 and 0.5 ml for I.V., P.V., and I.A. routes, respectively. The other ear of rabbits received vehicle (0.9% saline) in a similar fashion. All animals were observed for 9 days and then sacrificed. All ears (injection sites) were examined microscopically.

**Results:** No treatment related local irritation was evident when the drug was given via I.V., P.V., or I.A. routes. No histological abnormalities were evident at the injection sites, which could be attributed to treatment. Hence drug does not produce local irritation in rabbits.

A single I.V., paravenous (P.V.), or I.A. injection of 0.4% pantoprazole (free acid) into the ear did not produce local irritation in rabbits.

**Acute Dermal Irritation of B8610-023 in a Study With Rabbits (GTR-32026).**

**Testing Laboratories:** Byk Gulden
Inst. of Pathology and Toxicology
Hamburg, Germany

**Study Started:** May 7, 1992

**Study Completed:** April 13, 1993

**GLP Requirements:** A Statement of Compliance with GLP regulations was included.

**Animals:** New Zealand White female rabbits (about 2.9 kg).

**Methods:** Three female rabbits received dermal application of 0.5 g pantoprazole (moistened with distilled water). The applied sites were occluded with semi-occlusive dressing for 4 hours. An untreated skin area on each rabbit was used as a control. At 4 hour dressing were removed and test area was examined for irritation. On day 15 rabbits were killed and skin samples were examined microscopically.

**Results:** Only slight redness was seen in treated skin area which disappeared on days 4-8. No histopathological abnormalities were seen in treated skin on day 15 of the study. Hence, pantoprazole has very low potential of dermal irritation in rabbits.

Pantoprazole has a low potential of dermal irritation in rabbits.

**Acute Dermal Irritation Study with Rabbits with the Thiol Metabolite (B 8401-026) (GTR-32257).**

**Testing Laboratories:** Byk Gulden
Inst. of Pathology and Toxicology
Hamburg, Germany

**Dates Study Started and Completed:** July 9, 1991 and September 18, 1991.

**GLP Requirements:** A Statement of Compliance with GLP regulations was included.

**Animals:** New Zealand White Rabbits.

**Methods:** Three male rabbits received dermal application of 0.5 g of B 8401-026 (moistened with 1,2-propylene glycol). The applied sites were occluded with semi-occlusive dressing for 4 hours. An untreated skin area on each rabbit was used as control. At 4 hr dressing were removed and sites were examined at 0.5, 1, 24, 48 and 72 hr after removal of dressing for irritation. On day 15 rabbits were killed and skin samples examined microscopically.

**Results:** Only slight redness but no edema was seen in treated skin areas which disappeared on days 4-9 of the study. No histopathological abnormalities were seen in treated skin on day 15 of the study. Hence B 8401-026 has very low potential of dermal irritation in rabbits.

The thiol metabolite of pantoprazole (B8401-026) has a low potential of dermal irritation in rabbits.

**Acute Eye Irritation Test in Rabbits with the Thiol Metabolite (B 8401-026) (GTR-32258).**

**Testing Laboratories:** Byk Gulden
Inst. of Pathology and Toxicology
Hamburg, Germany

**Dates Study Started and Completed:** July 30, 1991 and September 20, 1991

**GLP Requirements:** A Statement of Compliance with GLP regulations was included.

**Animals:** New Zealand White Female Rabbits.

**Methods:** Three rabbits received 0.1 g (powder) of B 8401-026 in one of their conjunctival sac. The other eye of each rabbit was used as a control (untreated). Assessment of irritation was made at 1, 4, 24, 48 and 72 hours after the treatment.

**Results:** B 8401-026 was slightly irritant to the mucous membranes around the eye of rabbits.

The thiol metabolite of pantoprazole (B 8401-026) was slightly irritant to the mucous membranes around the eye of rabbits.

**Dog**

**Acute Intravenous and Perivenous Irritancy Study with Pantoprazole in the Dog (GTR-31993).**

**Testing Laboratory:** [redacted]

Byk Gulden
Konstanz, Germany

**Study Started:** November 16, 1997

**Study Completed:** March 1988 (Stamp Date of January 6, 1998)

**GLP Requirements:** Statements of compliance with GLP regulations and the Quality Assurance Unit were included.

**Animals:** One male (15 months, 16.8 kg) and one female (12 months, 9.2 kg) beagle dog were used in this study.

**Drug Batch:** Pantoprazole, [redacted]

**Methods:** For each dog, both cephalic and both saphenous veins were injected with pantoprazole (0.5 mL of a 4 mg/mL solution) or the vehicle. Immediately following intravenous administration of pantoprazole or vehicle, 0.5 mL of the same solution was administered by the perivenous route. Injection sites were observed prior to treatment and at 5, 24, and 48 hr after dosing.

**Results:** There were no signs of local irritancy following intravenous administration of pantoprazole (0.5 mL of a 4 mg/mL solution), immediately followed by paravenous administration of 0.5 mL of the same solution.

There were no signs of local irritancy following intravenous and paravenous administration of pantoprazole (0.5 mL of a 4 mg/mL solution).

**In Vitro Effects on Red Blood Cells**

**In Vitro Human and Canine Red Cell Hemolysis Study with Pantoprazole (GTR-31994).**

**Testing Laboratory:** [redacted]

Byk Gulden
Konstanz, Germany

**Study Started:** February 1987

**Study Completed:** March 15, 1988 (Stamp Date of January 6, 1998)

**GLP Requirements:** Statements of compliance with GLP regulations and the Quality Assurance Unit were included.

**Subjects:** Blood (20 mL) was collected from 6 apparently healthy human subjects. Blood (10 mL) was collected from six untreated beagle dogs, which appeared to be in good health.

**Drug Batch:** Pantoprazole, batch number 3

**Methods:** Red blood cell hemolysis was measured using the method of Reed and Yalkowsky (1985). Defibrinated blood obtained from human donors was incubated with an equal volume of 10 mg/mL pantoprazole, vehicle, 1 mg/mL saponin (positive control), or 0.9% NaCl solution for 2 or 30 min. To assess any effect on membrane permeability, the mean cell fragility of human and canine red blood cells was measured following exposure to 10 mg/mL pantoprazole, vehicle, or 0.9% NaCl.

**Results:** 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 4-17% hemolysis as compared to 0-7.0% for the vehicle. Mean cell fragility for dogs red blood cells was increased to 0.51 (% NaCl) following incubation in 10 mg/mL pantoprazole as compared to 0.447 (% NaCl) for the vehicle. Mean cell fragility for human red blood cells was unaffected by incubation with 10 mg/mL pantoprazole.

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.

**Effect of Pantoprazole on the Membrane Stability of Human, Rat, and Dog Erythrocytes (GTR-31992).**

**Testing Laboratory:** Byk Gulden
Konstanz, Germany

**Study Started:** July 1987

**Study Completed:** May 26, 1988 (Stamp Date of May 26, 1988)

**GLP Requirements:** No statements of compliance with GLP regulations or the Quality Assurance Unit were included.

**Subjects:** Human female, 60 kg; male beagle dog, 11 kg, and a female Sprague Dawley rat, 230 g.

**Drug Batch:** Pantoprazole, batch number K23/161

**Methods:** Red blood cells were purified from a female human subject, a male beagle dog, and a female Sprague Dawley rat. Hypotonic NaCl/phosphate buffer solutions, which produced approximately 50% hemolysis in 2 hr, were mixed with pantoprazole at concentrations ranging from $3 \times 10^{-8}$ to $3 \times 10^{-4}$ M, and the same stock erythrocyte suspension. After a 2-hr incubation period, the quantity of liberated hemoglobin was determined.

**Results:** Pantoprazole at concentrations of $3 \times 10^{-8}$ to $3 \times 10^{-5}$ M had no effect on hypotonic hemolysis of human, dog, or rat red blood cells. Pantoprazole at $3 \times 10^{-4}$ M reduced the relative hypotonic hemolysis of dog and rat erythrocytes by 15-20% and human erythrocytes by 30%.

Pantoprazole at concentrations of $3 \times 10^{-8}$ to $3 \times 10^{-5}$ M had no effect on hypotonic hemolysis of human, dog, or rat red blood cells. Pantoprazole at $3 \times 10^{-4}$ M reduced the relative hypotonic hemolysis of dog and rat erythrocytes by 15-20% and human erythrocytes by 30%.

**PROPOSED TEXT OF THE LABELING FOR PANTOPRAZOLE.**

The label is according to 21 CFR 201.50, Subpart B (April 1, 1998). However, the following changes should be incorporated:

**1. Clinical Pharmacology:**

Pharmacodynamics

*Enterochromaffin-Like (ECL) Cell Effects*

**Sponsor's Version:**

[redacted]

**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:**

[redacted]

**2. Carcinogenesis, Mutagenesis, Impairment of Fertility:**

**Sponsor's Version:**

**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.

**Proposed Version:**

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, 1 to 10 times the recommended human dose based on body surface area. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors.

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

3. Pregnancy:

Sponsor's Version:

***Teratogenic Effects***
***Pregnancy Category B***

**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.

**4. Nursing Mothers:**

**Sponsor's Version:**

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

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

**5. Overdosage:**

**Sponsor's Version:**

**Evaluation:** The text is not in accord with 21CFR, 201.50, Subpart B (April 1, 1998). The sponsor needs to be consistent in expressing the dose in terms of the free acid. In the text concerning data from acute toxicity studies, the sponsor used the sodium salt for expressing doses with mice and rats, but used the free acid for expressing the doses with dogs. All doses were changed to minimum lethal doses.

**Proposed Version:**

[redacted]

**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 oral or 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 oral or intravenous route inhibited histamine or impromidine ($H_2$ receptor agonist)-stimulated gastric acid secretion in the Heidenhain pouch beagle dog. Pantoprazole administered by the oral or the intraduodenal route inhibited the formation of gastric mucosal lesions induced by aspirin in the modified Shay rat. Inhibition of acid output paralleled antiulcer effect. Pantoprazole administered by the oral route to rats abolished gastric lesions induced by stress or acidified ethanol as well as gastric and duodenal ulcers induced by acetic acid. Pantoprazole administered by the oral route to rats completely prevented esophageal lesions induced by ligation of the pylorus and forestomach. 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 of no pharmacological activity as compared to the parent compound.

Pantoprazole (PROTONIX™) enteric-coated tablets are indicated for the short-term treatment (4 to 8 weeks) of gastroesophageal reflux disease. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of PROTONIX may be considered. The therapeutic dose of pantoprazole is 40 mg/day or 0.8 mg/kg for 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 the thiol metabolite of pantoprazole in rats; acute toxicity studies with ——— in mice and rats; two 4-week oral dose range finding toxicity studies in mice; four 4-week intravenous toxicity studies with pantoprazole in rats; a 4-week intravenous toxicity study with ——— in rats; two 4-week oral toxicity studies with pantoprazole in rats; a 3-month oral toxicity study with pantoprazole in aged rats; a 90-day dose range finding study with the thiol metabolite of pantoprazole in Fischer rats that included comparison to pantoprazole at 200 mg/kg/day; an electron microscopic examination of the rat liver after a 3-month treatment period with pantoprazole or its thiol metabolite; 6- and 12-month oral toxicity studies 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; 10- and 30-day oral toxicity studies in beagle dogs; 6- and 12-month oral toxicity studies in 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 and oral 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 ——— pulmonary toxicity studies with pantoprazole and its thiol metabolite in rats and beagle dogs; assessment of effects on the thyroid gland that included a study of thyroid hormone metabolism and UDPGT induction in pantoprazole-treated rats; two 4-week studies that examined levels of $T_3$, $T_4$, and TSH in pantoprazole-treated rats, and a 4-week study of thyroid function in pantoprazole-treated rats using the perchlorate discharge test; a 28-day electroretinographic study in cynomolgus monkeys; gastrin profile studies that consisted of a 4-week study with rats that compared the effects of pantoprazole with omeprazole and lansoprazole, a 30-day study that compared changes between Wistar and Sprague Dawley rats, and a 10-week study in rats that compared the effects of pantoprazole with omeprazole and lansoprazole; a 60-day toxicity study with rats that assessed changes in serum cholesterol levels; a 14-day toxicity study in rats to assess the mitogenic action of pantoprazole on the liver; 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/kg (equivalent to 0.8 mg/kg for a 50 kg person). Plasma AUC values for unchanged drug following a single oral administration of pantoprazole were as follows: $B6C3F_1$ mice that received doses from 25 to 150 mg/kg were observed with values ranging from ——— μg*hr/mL; Sprague Dawley rats that received doses from 5 to 1200 mg/kg were observed with values ranging from ——— μg*hr/mL; Fischer rats that received doses from 5 to 50 mg/kg were observed with values ranging from ——— μg*hr/mL, beagle dogs were that received doses of 7.5 to 100 mg/kg were observed with values ranging from ——— μg*hr/mL, and cynomolgus monkeys that received a dose of 5 mg/kg were observed with a value of 0.46 μg*hr/mL. Plasma AUC values for unchanged drug in healthy human male volunteers, who received a therapeutic dose of pantoprazole at 40 mg/day by the oral route ranged from ——— μg*hr/mL. Plasma AUC values for the parent compound were found to represent a small fraction of the total radioactivity suggesting extensive metabolism. Pantoprazole appeared to undergo extensive first pass metabolism and rapid elimination and bioavailability values displayed high variabiiity. Bioavailability of total radioactivity and parent drug following oral administration of pantoprazole to rats at 5 mg/kg were 66 and 31%, respectively. Bioavailability of parent drug in dogs following an oral dose of 60 mg/kg was 44%. Bioavailability of total radioactivity and parent drug following oral administration of 5 mg/kg pantoprazole to cynomolgus monkeys were 51.77 and 3.5%, respectively. It should be noted that bioavailability values in rats and dog appear to be high. The half-lives of the parent compound in most species were generally <1 hr. For studies with pantoprazole in healthy human male volunteers, bioavailability of an oral therapeutic dose at 40 mg/day ranged from 47.3 to 90.8%. For humans, little acid degradation of the drug occurred in the stomach and there was a low hepatic first-pass effect. The half-life of pantoprazole following oral or intravenous administration to human volunteers was approximately 1 hr. Non-linear toxicokinetics of pantoprazole may be due to reduced absorption at higher dose levels (i.e., dissolution rate limited absorption) or increased first-pass 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%. ——— studies with rats that received pantoprazole, with $^{14}C$-label located at the C-2 position of the benzimidazole ring, by the oral or 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 ——— 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 ≤ 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 ≤90% of drug-related compounds, while fecal excretion accounted for ≤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 (—— 97167) were the major circulating drug-related compounds detected in plasma for rats and dogs. The thiol metabolite (—— 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 desmethylhydoxylated 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 ( —— 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 was examined in mice, rats, and dogs. In mice that received pantoprazole by the oral route, the maximum nonlethal doses in both males and female mice were 750 and 500 mg/kg, respectively. The minimum lethal doses in male and female mice were 1000 and 750 mg/kg, respectively. Estimated oral $LD_{50}$ values in male and female mice were >1000 and 750 mg/kg, respectively. In male and female mice that received pantoprazole by the intravenous route, the maximum nonlethal and minimal lethal doses were 350 and 400 mg/kg, respectively. Estimated intravenous $LD_{50}$ values in male and female mice were 399 and 395 mg/kg, respectively. In rats that received pantoprazole by the oral route, the maximum nonlethal dose in both male and female rats was 700 mg/ kg/day. The minimum lethal dose in both male and female rats was 900 mg/ kg/day. Estimated oral $LD_{50}$ values in male and female rats were 1343 and 1037 mg/kg/ day, 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 $LD_{50}$ values in male and female rats were 200-331 and 256-343 mg/kg, respectively. In beagle dogs following oral administration of

pantoprazole, the maximum nonlethal and minimum lethal doses were 300 and 1000 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 $LD_{50}$ 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 $LD_{50}$ values in male and female mice were 244 and 220-270 mg/kg, respectively. The intravenous $LD_{50}$ value of the (-) enantiomer appears to be significantly lower than that observed for the (+) enantiomer or the racemate (estimated intravenous $LD_{50}$ 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 thiol metabolite of pantoprazole (B8401-026; 5-difluoromethoxy-1H-benzimidazole-2-thiol) has been associated with pulmonary toxicity in dogs. The acute oral toxicity of the thiol metabolite was assessed in rats at doses ranging from 160 to 810 mg/kg. The maximum nonlethal dose of the thiol metabolite of pantoprazole was 240 mg/kg in male rats and 160 mg/kg in female rats. The minimum lethal dose of the thiol metabolite of pantoprazole was 360 mg/kg in male rats and 240 mg/kg in female rats. The $LD_{50}$ values were 360 mg/kg for male rats and 340 mg/kg for female rats. Clinical signs included ataxia, loss of muscle tone, prostration, hypothermia, reduced activity, ptosis, piloerection and hunchbacked posture. Oral bioavailability of the thiol metabolite was not assessed. Evidence of pulmonary edema was observed in rats that received pantoprazole at oral doses ≥360 mg/kg. Histopathological analysis of the lungs from rats that received doses ≥360 mg/kg revealed protein-rich perivascular and focal alveolar edemas. Estimated oral $LD_{50}$ values for pantoprazole in male and female rats were 1343 and 1037 mg/kg/day, respectively. The acute toxicity of the thiol metabolite appears to be greater than that of pantoprazole.

The compound, ———————————, is an impurity found in the lyophilized formulation of pantoprazole for intravenous injection. The acute intravenous toxicity of ——— was examined in mice and rats. Mice received ——— at doses ranging from 50 to 400 mg/kg. Rats received ——— 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. $LD_{50}$ 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. $LD_{50}$ 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 $LD_{50}$ values for pantoprazole in male and female mice were 399 and 395 mg/kg, respectively. The estimated intravenous $LD_{50}$ values for pantoprazole in male and female rats were 200-331 and 256-343 mg/kg, respectively. The acute intravenous toxicity of ——— 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 4-week oral toxicity study, Sprague Dawley rats received pantoprazole at doses of 0, 1, 5, 20, and 500 mg/kg/day. Following the treatment period, selected rats from the control and 500 mg/kg/day groups entered an 8-week recovery period. The dose of 5 mg/kg/day could be considered a tolerated dose given that changes in the stomach, described below, were most likely due to the pharmacological actions of pantoprazole. Serum gastrin levels were elevated rats that received doses ≥5 mg/kg/day during the treatment; however, levels could not be determined during the recovery period due to technical problems. The stomach, thyroid gland, and spleen were the target organs of toxicity. In fundic region of the stomach, changes were observed as follows: an increased incidence of chief cell hyperplasia at doses ≥5mg/kg/day, an increased incidence of parietal cell hyperplasia at doses ≥5 mg/kg/day, and an increased incidence of parietal cell degeneration/vacuolation at doses ≥20 mg/kg/day. Parietal cell hyperplasia and degeneration/vacuolation were still evident for the male 500 mg/kg/day group at the end of the recovery period. The incidence of glandular epithelial cell degeneration was increased in the cardiac region of the stomach at a dose of 500 mg/kg/day and in the pyloric region of the stomach at doses ≥1 mg/kg/day. Glandular epithelial cell degeneration was not evident in these regions at the end of the recovery period. For the thyroid gland in female rats that received 500 mg/kg/day, epithelial cells in the follicle underwent a change in cell morphology from mainly flat follicle cells to mainly cuboidal follicle cells. This change of cell morphology was not evident at the end of the recovery period. For the spleen at doses ≥20 mg/kg/day, there was evidence of iron depletion. There were no findings of iron depletion at the end of the recovery period.

In a 4-week oral toxicity study, Sprague Dawley rats received pantoprazole at doses of 1, 5, and 500 mg/kg/day. Following the treatment period, rats in the control and 500 mg/kg/day groups entered an 8-week recovery period. This study was performed due to problems in measurements of plasma gastrin levels during the recovery period in the previous study; although, the dose of 20 mg/kg/day was omitted. Drug-related increases in plasma gastrin levels were observed in rats that received doses ≥1 mg/kg/day during the treatment period; however, there was not a dose response relationship. The elevation of gastrin with a dose of 1 mg/kg/day was observed on day 31. At the end of the first week of the recovery period, serum levels of gastrin were still significantly higher in high dose treated females compared to control values. After 4 and 8 weeks of the recovery period, serum gastrin levels had returned to normal. Overall effects of the drug on body weight, food consumption, hematology, organ weight, and histopathology (stomach and spleen) were similar to that seen in the previous study.

In a 4-week oral toxicity study, Sprague Dawley rats received the thiol metabolite of pantoprazole (B8401-026) at doses of 0, 15, 50 and 150 mg/kg/day for 4 weeks. The no effect dose was identified as 15 mg/kg/day. Reductions in heart rate and significant increases in the Q-T intervals were observed for male and female rats at 150 mg/kg/day. The P-Q interval was significantly higher for male rats at 150 mg/kg/day. Electrocardiogram abnormalities have not been observed in studies with pantoprazole. The target organs of toxicity were the liver, thyroid gland, pituitary gland, and adrenal gland. Histopathological changes for these tissues were confined to 50 and 150 mg/kg/day. Histopathological changes at doses of 50 and 150 mg/kg/day consisted of an increased incidence of centrilobular hepatocellular hypertrophy for the liver, diffuse follicular hyperplasia for the thyroid gland, hyperplasia and hypertrophy of "throtroph cells" for the pituitary gland. and

an increased incidence (and severity) of vacuolation and degeneration of the adrenal cortex. At 150 mg/kg/day, an increased incidence (and severity) of tubular regeneration in the kidneys, pelvic uroliths and chronic pyelitis were found. Evidence of renal damage at 150 mg/kg/day also included elevations of serum urea and creatinine and increased urinary excretion of $Ca^{2+}$, $Cl^-$, and $Na^+$. There were no histopathological changes found in the heart tissue that corresponded to observed electrocardiographic changes. Electrocardiographic abnormalities as well as histopathological changes observed in the pituitary gland, adrenal gland, and kidney have not been found with pantoprazole. The thiol metabolite possesses a different spectrum of toxicity as compared to pantoprazole and may be potentially more toxic.

In a 3-month oral toxicity study, female rats of three different strains (i.e., Sprague-Dawley, Wistar and Fischer), starting at 52-57 weeks of age, received pantoprazole at doses of 0, 0.8 and 4 mg/kg/day. The objective of this study was to delineate differences in response to pantoprazole treatment among these three strains with regard to possible selection of one for the rat carcinogenicity study. The dose of 0.8 mg/kg/day could be considered a tolerated dose as observed stomach changes, described below, were most likely due to the pharmacological action of the drug. Histopathological examination of the stomach, liver, lungs and thyroids was performed for all groups. The stomach, liver, and thyroid gland were the target organs of toxicity. In the gastric fundus, parietal cell hyperplasia, foveolar hyperplasia, chief cell hyperplasia, and atypical eosinophilic chief cells were observed at a dose of 4 mg/kg/day for all rat strains. Foveolar hyperplasia and chief cell hyperplasia were also evident for Wistar and Fischer rats at a dose of 0.8 mg/kg/day. The number of Grimelius-positive cells increased dose-dependently for all rat strains. For the liver, peribiliary inflammation and bile duct proliferation were observed in Sprague Dawley and Wistar rats that received 4 mg/kg/day. For the thyroid gland, the follicular epithelium was slightly increased in Wistar rats that received 4 mg/kg/day. Proliferation of C-cells was evident in all strains at 4 mg/kg/day and for Fischer rats at 0.8 mg/kg/day.

A 90-day oral dose range finding study with the thiol metabolite of pantoprazole (B8401-026) was conducted in Fischer 344 rats to identify suitable doses for a 2 year carcinogenicity study in rats [redacted]). Rats received B8401-026 by oral gavage at doses of 0, 20, or 50 mg/kg/day. For comparison, rats were treated pantoprazole by oral gavage at a dose of 200 mg/kg/day. B8401-026 at 50 mg/kg/day appeared to be well tolerated. There were no treatment-related effects on body weight gain for male or female rats that received either B8401-026 or pantoprazole. Target organs of toxicity for both B8401-026 and pantoprazole included the stomach, thyroid gland, lungs, and liver. Thyroid gland activation was observed for male and female rats that received B8401-026 at 20 and 50 mg/kg/day. In contrast, the incidence of the thyroid gland activation for male and female rats that received pantoprazole at 200 mg/kg/day was lower. Changes in the glandular stomach in the fundic region for male and female rats that received B8401-026 at 50 mg/kg/day included glandular ectasia and/or parietal cell swelling in the gastric mucosa. Changes in the glandular stomach in the fundic region for male and female rats that received

pantoprazole at 200 mg/kg/day included parietal cell swelling, parietal cell degeneration/ vacuolation, chief cell hyperplasia, eosinophilic chief cells, glandular ectasia, inspissated secretory products and a mild lymphocytic infiltration of the submucosa. Grimelius-positive cell (GPC) hyperplasia was observed in the stomach for male and female rats that received pantoprazole at 200 mg/kg/day. For the liver, centrolobular swelling was observed for male and female rats that received either B8401-026 at 50 mg/kg/day or pantoprazole at 200 mg/kg/day. Round/mixed cell infiltration and alveolar histiocytosis were observed in the lung for male and female rats that received either B8401-026 at 50 mg/kg/day or pantoprazole at 200 mg/kg/day. B8401-026 at 20 or 50 mg/kg/day increased uridyldiphosphoglucuronyl transferase activity for both male and female treatment group. B8401-026 at 20 and 50 mg/kg/day decreased ethylmorphine demethylase activity for male treatment groups in a dose-related manner; although, activities for female treatment groups were unchanged. Effects of B8401-026 at 20 or 50 mg/kg/day on the activities of lonazolac hydroxylase and 7-ethoxycoumarin dealkylase for both male and female treatment groups were relatively small. In contrast, pantoprazole at 200 mg/kg/day increased the activities of lonazolac hydroxylase, 7-ethoxycoumarin dealkylase, and uridyldiphosphoglucuronyl transferase in both male and female treatment groups. Pantoprazole increased ethylmorphine demethylase activity for the female treatment group; although, it was unchanged for the male treatment group. Histopathological observations of centrolobular swelling in the liver appear to correlate with increased hepatic cytochrome P450 activity. For pantoprazole at 200 mg/kg/day, based upon no mortality, no impairment of body weight gain, and observed histopathological changes, this dose could be considered a maximum tolerated dose in Fischer 344 rats.

In 3-month oral toxicity studies with pantoprazole or its thiol metabolite (B8401-026) in Fischer 344 rats, sections of the liver were collected for electron microscopical evaluation. Rats received pantoprazole at 50 or 200 mg/kg/day or B8401-026 at 50 mg/kg/day. Rats were also included that received either pantoprazole at 200 mg/kg/day or B8401-026 at 50 mg/kg/day for 3 months followed by an 8-week recovery period. Electron Microscopic examinations of the liver of pantoprazole or B8401-026 treated rats revealed increases in endoplasmic reticulum (related to induction of P450 isozymes), cell membrane turnover, intracellular cholesterol storage and bile secretion. These findings were mostly reversible after a 8 week recovery period in pantoprazole-treated rats, while reversibility was not complete in B8401-026 treated rats. There was no evidence of peroxisomal proliferation in the liver of any treatment group.

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. Additional animals were assigned to the control and 320 mg/kg/day groups for an 8-week recovery period. The dose of 4 mg/kg/day could be considered a tolerated dose given that stomach changes, described below, were more than likely a result of the pharmacological action of the drug. Final body weight was impaired by >10% for only female rats at 320 mg/kg/day. During the treatment period at all sampling times, gastrin levels were elevated at doses ≥4 mg/kg/day. During the recovery period, gastrin levels were elevated in the 320 mg/kg/day group at week 1, but not at week 8. The stomach, liver, thyroid gland, and spleen were the target organs of toxicity. For the fundic region of the stomach, increased incidences of chief cell hyperplasia and

inspissated secretory products occurred at doses ≥0.8 mg/kg/day. An increased incidence of chief cell atrophy was found at doses ≥0.8 mg/kg/day. An increased incidence of parietal cell degeneration/vacuolation and cell infiltrates was found primarily for rats that received 320 mg/kg/day. The incidence of parietal cell hyperplasia was increased for rats that received 4 and 16 mg/kg/day, but decreased at 320 mg/kg/day. Parietal cell hyperplasia and inspissated secretory products persisted through the recovery period. Other changes were not found at the end of the recovery period. For the forestomach, there was an increased incidence of hyperkeratosis for rats that received 320 mg/kg/day; however, this change was not observed at the end of the recovery period. For the liver at the end of the treatment period, centrolobular swelling of hepatocytes was observed for male rats at doses ≥0.8 mg/kg/day and female rats at 320 mg/kg/day. Bile duct hyperplasia was observed for male rats at 320 mg/kg/day. For male rats that received 320 mg/kg/day, there was little or no hemosiderin storage. For female rats that received 320 mg/kg/day, there was reduced or no fat staining. A hepatocellular adenoma was seen in 1/24 male rats treated with 320 mg/kg/day. Centrolobular swelling of hepatocytes was not found at the end of the recovery period; however, bile duct hyperplasia (male rats), lack of hemosiderin storage (male rats), and reduced or no fat staining (female rats) persisted. For thyroid gland, epithelial cells of the thyroid follicles underwent a change in cell morphology to cuboidal and columnar features for female rats at 16 and 320 mg/kg/day. Normal cell morphology was observed at the end of the recovery period. 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. For the spleen, there was a depletion of iron levels at the end of the treatment period for male rats at 320 mg/kg/day. This change persisted through the recovery 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. The dose of 5 mg/kg/day could be considered a tolerated dose as stomach changes, described below, were more than likely due to the pharmacological action of the drug. Final body weight was impaired by >10% in female rats that received 300 mg/kg/day. Serum gastrin, cholesterol, and triglyceride levels were elevated at doses ≥ 5 mg/kg/day during the treatment period. The stomach, liver, thyroid gland, spleen, and kidney were the target organs of toxicity at the end of the treatment period. For the stomach at doses ≥ 5 mg/kg/day, findings were increased height of fundic mucosa, fundic gland ectasia, eosinophilic chief cells (fundus), mixed inflammatory cell infiltrate (fundus), mild fibrosis of the lamina propria ( fundus), and hyperplasia of chromogranin-positive cells (fundus). Diffuse and focal ECL cell hyperplasia were evaluated separately and correlated to histomorphometric measurements of fundic mucosal height. The diffuse ECL cell index was increased at a dose of 5 mg/kg/day; however, the index decreased with increasing dose. In contrast, focal hyperplasia was more prominent at 300 mg/kg/day than at 5 mg/kg/day. For the stomach at doses ≥50 mg/kg/day in male rats, focal squamous cell hyperplasia (non-glandular stomach) was observed. For the liver at doses ≥ 5 mg/kg/day, centrilobular hepatocellular hypertrophy was observed. Hepatocellular necrosis was observed at doses ≥50 mg/kg/day. Additionally, one low dose treated male had a hepatocellular adenoma and another low dose male had

a hepatocellular carcinoma. For the thyroid gland at doses ≥50 mg/kg/day, follicular cell hypertrophy was observed. For the spleen at doses ≥50 mg/kg/day, there was reduced hemosiderin. For the kidney, the incidence of mild to severe nephropathy was increased at doses ≥ 50 mg/kg/day. The incidence of urothelial hyperplasia was increased at a dose of 300 mg/kg/day. Changes the kidney correlated with increased incidences of proteinuria at 50 and 300 mg/kg/day. At the end of 9-month recovery period, minimal fundic gland ectasia and minimal eosinophilic chief cells in the fundic mucosa were observed in rats that had received pantoprazole at 5 mg/kg/day. Additionally, a malignant neuroendocrine cell tumor (fundus) was observed for 1 of 11 female rats at 5 mg/kg/day. For rats that had received 5 mg/kg/day, there was no evidence of increased fundic mucosal height and hyperplasia of chromogranin-positive cells at the end of the recovery period. 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 the 1-year chronic oral toxicity study with rats, serum cholesterol levels were increased dose-dependently. Serum cholesterol levels in short term toxicity studies were not monitored. In the present study sponsor assessed the time course of the increase in total serum cholesterol in rats after drug administration. Male rats received pantoprazole by oral gavage at doses of 0 or 300 mg/kg/day for 60 days. Cholesterol levels were significantly elevated on days 15, 30, and 60 in rats that received pantoprazole at 300 mg/kg/day.

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 —— 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 triiodothyreonine, thyroxin, 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.

In a 10-day oral toxicity study, beagle dogs received pantoprazole in either enteric-coated tablets at doses of 75 and 100 mg/kg/day or uncoated tablets at doses of 50, 75, 100, and 150 mg/kg. There was 1 dog/sex/group. For the surviving male dog receiving enteric-coated tablets at 100 mg/kg/day, the dose was reduced to 75 mg/kg/day on day 5. Group receiving the uncoated tablets at 50 and 75 mg/kg/day were added after the start of the study due to toxicity observed in the other groups. The following dogs died or were sacrificed in moribund condition during the treatment period: females that received the enteric-coated formulation at 75 or 100 mg/kg/day, the male and female that received the uncoated formulation at 100 mg/kg/day, and the female that received the uncoated formulation at 50 mg/kg/day. Necropsy examinations of all dogs that were found dead or sacrificed in a moribund condition during the treatment period were found to have evidence of pulmonary edema. Histopathological analysis of the lungs from these dogs revealed effusion of fluid into the pulmonary alveoli. Findings included foamy alveolar macrophages and eosinophilic material in alveoli suggestive of proteinaceous fluid. In dogs that received uncoated tablets at doses of 75 and 100 mg/kg/day, there were also findings of peribronchiolar/perivascular edema and edema of the mediastinal structures (i.e.. thymus, heart/pericardium, and esophagus). Dogs sacrificed after 10 days of treatment showed no evidence of pulmonary edema. Minimal to moderate parietal cell vacuolation was found in the stomach for most of the dogs. The sponsor speculated that pulmonary toxicity induced by pantoprazole was most severe on days 3 to 5; however, if the effects were not severe enough to be fatal, resolution occurred with continued dosing by day 10. Further, the sponsor speculated that pulmonary toxicity may be related to the supplier, with dogs supplied by ——— being more sensitive than those supplied by ——— although, later studies showed that pulmonary toxicity in dogs had little relationship to supplier.