≥3.83 mg/kg. The ED_{50} was determined to be 1.0 mg/kg. Only slight acid-induced breakdown of pantoprazole appeared to occur, suggesting that toxicity studies in rats can be performed without the use of a protective dose of bicarbonate.

Effect on Gastric Acid Secretion Stimulated by Histamine in Fistula Rats (GTR-31421).

Pantoprazole at ≥ 5 mg/kg (intraduodenal administration) completely inhibited acid secretion stimulated by histamine in fistula rats.

Influence of Pantoprazole on 2-DG-Stimulated Gastric Secretion in the Anesthetized Rat with Gastric Fistula (GTR-31441).

A 2 hr pretreatment with pantoprazole administered by the oral route at doses of 0.625, 1.25, 2.5, and 7.5 mg/kg produced a dose-related inhibition of 2-deoxy-d-glucose-induced gastric acid secretion in female Sprague Dawley rats with gastric fistulas. ED_{50} values for inhibition of acid output, acid secretion, and secretion volume were 1.73, 6, and 3.7 mg/kg, respectively. The inhibitory effect of pantoprazole was predominantly on volume of secretion rather than acid concentration.

Influence of Pantoprazole on Bethanechol-Induced Gastric Secretion and Salivation of the Anesthetized Rat (GTR-31443).

A 2 hr pretreatment with pantoprazole administered by the oral route at doses of 0.5, 2.5, and 5.0 mg/kg produced a dose-related inhibition of bethanechol (subcutaneous dose of 0.75 mg/kg)-induced gastric acid secretion in female Sprague Dawley rats with gastric fistulas. ED_{50} values for inhibition of secretory volume, acid output, and acid concentration were 1.6, 0.7, and > 5 mg/kg, respectively. Pantoprazole had no effect on salivation. Pantoprazole inhibited bethanechol-induced gastric acid secretion primarily due to decreased secretory volume.

Effects on Gastric Acid Secretion and Gastric Lesions in "Modified Shay Conscious SD Rat" (GTR-31464).

In this model, pantoprazole (130 μmole/kg/day = 50 mg/kg/day for 3 days) and omeprazole (40 μmole/kg/day = 138 mg/kg/day for 3 days) administered by the oral route, both inhibited gastric acid secretion (25% and 22%, respectively) and gastric lesions (76% and 66%, respectively). Data also indicated that in this model, pantoprazole was 3 times more potent then omeprazole.

Rat-Intravenous

Antisecretory Activity of the Two Enantiomers of Pantoprazole in the Pentagastrin-Stimulated Lumen-Perfused Rat Stomach In Vivo After I.V. Dose (GTR-31439).

In rats, acid secretion was stimulated by pentagastrin infusion (1 μg/kg/min). Sixty min after the start of pentagastrin, rats were given pantoprazole [(+) enantiomer B9010-007 or (-)enantiomer B9010-026: 0.04, 0.12, or 0.38 mg/kg by the intravenous route]. The two enantiomers of pantoprazole inhibited pentagastrin-induced gastric acid secretion in a dose-dependent manner. The intravenous ED_{50} values of the (+) and (-) enantiomers were 0.15 and 0.145 mg/kg, respectively.

Influence of Pantoprazole on 2-DG-Stimulated Gastric Secretion in the Anesthetized Rat with Gastric Fistula (GTR-31440).

A 30 min-pretreatment with pantoprazole, administered by the intravenous route at doses of 0.25, 0.375, 0.5, 0.625, and 0.75 mg/kg, inhibited 2-deoxy-d-glucose-stimulated gastric secretion Observed inhibition was not proportional to dose. Secretory volume was decreased, but acid concentration was unaffected. The ED_{50} values for inhibition of secretory volume and acid output were identical at 0.25 mg/kg.

Influence of Pantoprazole I.V. on Bethanechol-Induced Gastric Secretion and Salivation of the Anesthetized Rat (GTR-31442).

Pantoprazole administered by the intravenous route at doses of 0.1, 0.25, 0.5, and 1.0 mg/kg inhibited bethanechol (0.75 mg/kg, subcutaneous route)-induced gastric acid secretion in a dose-dependent manner in female Sprague Dawley rats with gastric fistulas. Pantoprazole was administered 30 min after bethanechol treatment. ED_{50} values for inhibition of secretory volume and acid output were identical at 0.5 mg/kg. The decrease in acid output appeared to be due to a decrease secretory volume. The acidity (acid concentration) of secretion was unaffected. Bethanechol-induced salivation was unaffected by pantoprazole treatment.

Antisecretory Activity and Duration of Action of Pantoprazole I.V. in the Pentagastrin-Stimulated Lumen-Perfused Rat Stomach In Vivo (Ghosh-Schild Rat) (GTR-31422).

Pantoprazole administered by the intravenous route at doses of 0.12, 0.23, 0.38, and 1.15 mg/kg inhibited pentagastrin (1 μg/kg/min IV)-induced gastric acid secretion in a dose-dependent manner in female Sprague Dawley rats implanted with gastric cannulas (Ghosh and Schild method). Duration of effect was also dose-dependent. The ED_{50} values for inhibition of pentagastrin-induced increase in HCl-secretion maximum and average 3.5 hr test) were 0.16 and 0.23 mg/kg, respectively.

Antisecretory Activity and Duration of Action of BYK18508 in the Pentagastrin-Stimulated, Lumen-Perfused Rat Stomach In Vivo (Ghosh-Schild Rat) After Intravenous Administration (GTR-32830).

BYK18508, the degradation product of pantoprazole-lyophilizate, administered by the intravenous route at dose a of 11.9 mg/kg to female Sprague Dawley rats, with implanted gastric cannulas, inhibited pentagastrin-induced gastric acid secretion to a maximum of 21%. Inhibition occurred 30 min after drug administration and persisted for 135 min. A lower dose of 4 mg/kg was inactive.

Influence of B8610-014 on the Acid Secretion in the Pentagastrin-Stimulated Lumen-Perfused (Ghosh-Schild rat) After Intravenous Administration (GTR-33306).

B8610-014, the sulfone metabolite of pantoprazole, administered by the intravenous route at dose of 39.94 mg/kg to female Sprague Dawley rats, with implanted gastric cannulas, had no effect on pentagastrin-induced gastric acid secretion.

Antisecretory Activity and Duration of Action of Lansoprazole in the Pentagastrin-Stimulated Lumen-Perfused Rat Stomach In Vivo (Ghosh-Schild Rat) After Intravenous Administration (GTR-33444).

Lansoprazole administered by the intravenous route at doses of 0.04, 0.11, 0.22, 0.37, and 0.74 mg/kg to female Sprague Dawley rats, with implanted gastric cannulas, inhibited pentagastrin-induced gastric acid secretion in a dose- and time-dependent manner. ED_{50} values for the maximal effect and average effect during the 3.5 hr test were 0.14 and 0.24 mg/kg, respectively.

Dog-Oral

Influence of Oral Administration of a Solution of Pantoprazole on Impromidine (H_2 Receptor Agonist)-Stimulated Gastric Secretion in the Heidehain Pouch Dog (GTR-31444).

Pantoprazole administered by the oral route in gelatin capsules at doses of 1.04, 2.08, and 4.16 mg/kg inhibited impromidine (H_2 receptor agonist)-stimulated gastric acid secretion in the Heidenhain pouch dog (i.e., a denervated gastric pouch that responds to humorally-mediated stimulation of gastric acid secretion, but not to CNS-mediated nervous stimulation, since vagal nerve fibers reaching the pouch have been surgically severed). Impromidine (2 μg/kg/hr) was infused continuously for 6 hr. Pantoprazole was administered 2 hr after the start of the infusion. ED_{50} values for inhibition of impromidine-stimulated gastric acid secretion were 3.11 mg/kg for 0-60 min, 1.55 mg/kg for 61-120 min, and 1.59 mg/kg for both 121-180 and 181-240 min.

The Effects of Pantoprazole After Intravenous, Intraduodenal, and Oral Administration on Histamine-Stimulated Gastric Acid Secretion in the Conscious Heidenhain Pouch Dog (GTR-31446).

The effects of pantoprazole, administered by either the intravenous, oral, or intraduodenal routes, on histamine-stimulated gastric acid secretion, were assessed in the Heidenhain pouch beagle dog. Histamine (0.15 mg/kg/hr) was administered by continuous intravenous infusion for periods up to 5 hr. Intravenous doses at 0.38 and 1.53 mg/kg caused 32 and 39% inhibition of acid output, respectively, on the first day of histamine challenge. On the second day of histamine challenge, inhibition of acid output was 14 and 57%, respectively, relative to the pretreatment value on day 1. Pantoprazole can exert significant inhibitory activity at 24 hr after intravenous dosing. An intraduodenal dose of 0.77 mg/kg produced a peak 48% inhibition of acid output at 1.5 hr after dosing. Oral doses in gelatin capsules at 1.53 and 3.83 mg/kg caused 28.5 and 71% inhibition of acid output, respectively. Peak inhibition occurred at 2.5 to 2.75 hr following oral dosing. Comparison of inhibition obtained with the intraduodenal and oral routes suggested that pantoprazole underwent acid degradation in the stomach. Pantoprazole administered by either the intravenous, oral, or intraduodenal routes was able to inhibit histamine-stimulated gastric acid secretion.

Effect of Pantoprazole Tablets vs Solution on the Intragastric pH in Dog With Gastric Fistula (GTR-31447).

Oral administration of 1.15 mg/kg of pantoprazole (enteric-coated tablet or solution) had no effect on intragastric pH on day 1 of the study. However, after 5 daily doses, both formulations increased intragastric pH in dogs with equal potency (maximum pH: 4-5).

Influence of Oral Administration of Enteric Coated Tablets of Pantoprazole on Impromidine (H_2 Receptor Agonist)-Stimulated Gastric Secretion in the Heidenhain Pouch Dog (GTR-31448).

Oral administration of pantoprazole formulated in enteric-coated tablets at doses of 1.03 and 2.06 mg/kg to Heidenhain pouch beagle dogs inhibited impromidine (H_2 receptor agonist)-stimulated gastric acid output by 43.0 and 46.4% by 4 hr after dosing, respectively.

Comparison of the Effect of Uncoated and Enteric Coated Tablets of Pantoprazole on the Intragastric 24 Hour pH Profile in the Gastric Fistula Dog (GTR-31449).

Oral administration of pantoprazole at 8.5 mg/kg formulated either as uncoated or enteric coated tablets elevated intragastric pH to approximately 4 in male beagle dogs with gastric fistulas; although, the time courses of action were significantly different. Onset of activity for uncoated tablet was 1 hr, while for enteric coated tablets, it was delayed until 2-3 hr. Uncoated tablets elevated intragastric pH to ~4 for approximately 9 hr, with a maximal effect obtained at 6 hr after dosing. Enteric coated tablets also elevated intragastric pH to ~4 for 10 hr; although, maximal effect was not obtained until 9 hr after dosing.

Influence of Oral Administration of Uncoated Tablets of Pantoprazole on Impromidine (H_2 Receptor Agonist)-Stimulated Gastric Secretion in the Heidenhain Pouch Dog (GTR-31450).

Pantoprazole administered by the oral route in gelatin capsules at doses of 1.15 and 2.30 mg/kg inhibited impromidine (H_2 receptor agonist)-stimulated gastric acid secretion in Heidenhain pouch beagle dogs in a dose-related manner. Impromidine (2 μg/kg/hr) was continuously infused by the intravenous route for 330 min. Pantoprazole was administered 90 min after the start of the infusion. ED_{50} values for inhibition of acid output were 4.3 mg/kg for 0-60 min, 1.55 mg/kg for 61-120 min, 1.29 mg/kg for 121-180 min, and 1.24 mg/kg for 181-240 min. The decrease in acid output was attributed to decreases in volume and acid concentration.

Dog-Intravenous

Influence of Intravenous Administration of Pantoprazole on the Intragastric 24 Hour pH-Profile in the Gastric Fistula Dog (GTR-31420).

I.V. administration of 0.95, 1.9 and 3.8 mg/kg of pantoprazole rapidly and dose-dependently increased intragastric pH in dog (maximum pH 4-5), and the slope of increase was comparable at these dose levels. Antisecretory effects persisted for 6-8 hr. A dose of 0.38 mg/kg of pantoprazole had no effect on intragastric pH in this experiment.

Influence of Pantoprazole on Impromidine (H_2 Receptor Agonist)-Stimulated Gastric Acid Secretion in the Heidenhain Pouch Dog (GTR-31445).

Pantoprazole administered by the intravenous route at doses of 0.125, 0.25, and 0.5 mg/kg inhibited impromidine (H_2 receptor agonist)-stimulated gastric acid secretion in the Heidenhain pouch beagle dog in a dose-related manner. Impromidine (2 μg/kg/hr) was continuously infused by the intravenous route for 330 min. Pantoprazole was administered 90 min after the start of the infusion. ED_{50} values for inhibition of acid output were 0.27 mg/kg for 0-60 min, 0.20 mg/kg for 61-120 min, and 0.17 mg/kg for 121-180 min.

Pantoprazole Elevates Intragastric pH for a Prolonged Period when Administered Under Conditions of Stimulated Gastric Acid Secretion in the Gastric Fistula Dog (GTR-31451).

The duration of the increased intragastric pH induced by pantoprazole (3.83 mg/kg, IV) during subcutaneous infusion of pentagastrin to fed dogs with gastric fistulas was significantly reduced by pretreatment with famotidine (data presented graphically). However, maximum pH-elevation induced by pantoprazole was not affected by pretreatment of dogs with famotidine. The data suggested that pantoprazole required activation in the acidic compartment of the parietal cell to produce a sustained intragastric pH-elevation.

Effect of I.V. Administration of Pantoprazole on Intragastric 24-hr pH Profile in the Fed Gastric Fistula Dog During Continuous S.C. Pentagastrin Infusion (GTR-31453).

Intravenous administration of pantoprazole at doses of 0.43, 1.3, and 4.32 mg/kg, dose-dependently, increased intragastric pH up to values between 5 - 6 during pentagastrin subcutaneous infusion. The duration of intragastric pH-elevation also increased dose-dependently.

Effects on Experimental Ulcers

Rat-Oral

Effect on Gastric Lesions Induced by Aspirin in Rats (GTR-31454).

Pantoprazole (10-80 mg/kg, p.o.) dose-dependently inhibited the gastric mucosal lesions induced by aspirin in rats.

Influence of Oral Pantoprazole on Gastric Secretion and on Gastric Lesions Induced by Oral Administration of 100 mg/kg of Acetylsalicylic Acid and Pylorus Ligature in the Conscious Rat (Modified Shay Rat) (GTR-31455).

Pantoprazole (0.03, 0.1, 0.3, 0.6, 1.0, 1.5, 2, 3, and 6 mg/kg) administered by oral gavage at doses ≥ 0.6 mg/kg inhibited the formation of gastric mucosal lesions, induced by aspirin (100 mg/kg) in the modified Shay rat, in a dose-dependent manner. ED_{50} values for inhibition of ulcer formation, secretory volume, and acid output were 0.23, 2.38, and 0.90 mg/kg, respectively.

Influence of Intraduodenal Pantoprazole on Gastric Secretion and on Gastric Lesions Induced by Oral Administration of 100 mg/kg Acetylsalicylic Acid and Pylorus Ligature in the Conscious Rat (Modified Shay Rat) (GTR-31457).

Pantoprazole (0.12, 0.38, 1.15, and 2.3 mg/kg) administered by the intraduodenal route at doses ≥ 0.38 mg/kg inhibited the formation of gastric mucosal lesions, induced by aspirin (100 mg/kg) in the modified Shay rat, in a dose-dependent manner. ED_{50} values for inhibition of ulcer formation, secretory volume, and acid output were 0.25, 1.55, and 0.87 mg/kg, respectively. Inhibition of gastric mucosal lesions paralleled inhibition of gastric acid secretion and acid output.

Duration of Antiulcer and Antisecretory Activity of Oral Pantoprazole in the Modified Shay Rat (GTR-31459).

Pantoprazole administered by the oral route at doses of 1, 1.5, 2, 3, and 6 mg/kg at 1 and 6 hr prior to ligation of the pylorus and oral administration of 100 mg/kg aspirin strongly inhibited the formation of gastric mucosal lesions. Inhibition of acid output paralleled antiulcer effect when pantoprazole was administered at 1 or 6 hr. However, when pantoprazole was administered 24 hr prior to ligation of the pylorus and oral administration of 100 mg/kg aspirin, only 6 mg/kg had an antiulcer effect. None of the pantoprazole doses had a significant inhibition of acid output at 24 hr after administration.

Effect on Gastric Lesions Induced by 7 hr-Water-Immersion Restraint Stress in Rats (GTR-31458).

Pantoprazole at ≥ 10 mg/kg completely abolished gastric lesions induced by 7 hr-water immersion restraint stress in rats.

Effect on Gastric Lesions Induced by-Acidified Ethanol in Rats (GTR-31460).

Pantoprazole (10-80 mg/kg, p.o.) dose-dependently inhibited the gastric mucosal lesions induced by acidified ethanol in rats.

Influence of Pantoprazole on Acetic Acid-Induced Gastric and Duodenal Ulcers in Rats (GTR-31461).

In rats, gastric and duodenal ulcers were produced by applying 80% acetic acid to "serosa" of stomach for 15 or 45 sec. Rats were treated orally twice daily with pantoprazole (pH 9) at daily doses of 1.2, 2.7, 5.4, 10.7, 21.5 or 42.9 mg/kg/day for 9 days. Pantoprazole at doses ≥ 10 mg/kg elicited a dose-related healing effect on acetic acid-induced gastric and duodenal ulcers. Pantoprazole inhibited acetic acid induced gastric and duodenal ulcers with ID_{50} values of 4.2 and 1.9 mg/kg/day, respectively.

Effect of Pantoprazole on Gastric Lesions Induced by 16-hr Water-Immersion Restraint Stress in Rats (GTR-31462).

Administration of pantoprazole by the oral route at doses ≥ 10 mg/kg produced a 100% inhibition of stressed-induced ulcers in rats. Stress was induced by immobilization and immersion of rats in cold water (23°C) to the level of xiphoid process for 16 hr. Omeprazole at 20 mg/kg produced a similar inhibition of stress-induced ulcers.

Effect on Pantoprazole or Omeprazole on Esophageal Lesions Induced by Both Pylorus and Forestomach Ligations in Rats (GTR-31463).

Pantoprazole at ≥ 3 mg/kg completely prevented esophageal lesions induced by ligation of the pylorus and forestomach, while omeprazole at doses ≥ 30 mg/kg were required to completely block esophageal lesions in rats.

Antisecretory and Antiulcer Effect of Pantoprazole Following a 3-Day Oral Administration in the Modified Shay Rat (GTR-33433).

The effects of pantoprazole on gastric acid secretion and ulcer formation were compared on aspirin-induced gastric lesions in female Sprague Dawley rats whose pylorus were occluded by ligation (Modified Shay rat). Pantoprazole at 50 mg/kg/day was administered by the oral route for 3 days. Pylorus ligation was performed 24 hr after the last dose. Four hr after pylorus ligation, gastric secretions were collected and mucosal lesions were graded. Pantoprazole at 50 mg/kg/day inhibited ulcer formation by 74% and acid output by 27%.

Rat-Intravenous

Influence of Intravenous Pantoprazole on Gastric Secretions and on Gastric Lesions Induced by Oral Administration of 100 mg/kg of Acetylsalicylic Acid and Pylorus Ligature in the Conscious Rat (Modified Shay Rat) (GTR-31456).

Administration of pantoprazole (0.04, 0.12, 0.38, 0.72, and 1.15 mg/kg) by the intravenous route at doses ≥ 0.12 mg/kg inhibited the formation of gastric mucosal lesions, induced by 100 mg/kg aspirin in the modified Shay rat, in a dose-dependent manner. Inhibition of gastric mucosal lesions paralleled inhibition of gastric acid secretion; although, doses ≥ 0.6 mg/kg were required to produce an antisecretory effects.

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.

Secondary Pharmacology

Gastrointestinal Pharmacology

Mouse-Oral and Intravenous

Effects of Oral and Intravenous Pantoprazole on Gastrointestinal Motility of Female Mice (GTR-31483 and GTR-31484).

Administration of pantoprazole by the oral route at doses of 3 to 300 mg/kg had no effect on intestinal propulsion in fasted female mice; however, oral doses of 100 and 300 mg/kg delayed the emptying of a charcoal suspension from the stomach. Administration of pantoprazole by the intravenous route at doses of 30 and 100 mg/kg had no effect on gastric emptying or intestinal propulsion in fasted female mice.

Rat-Oral

The Influence of Pantoprazole on Gastrointestinal Motility in the Rat (GTR-31482).

Administration of pantoprazole by the oral route at doses of 5, 20, and 60 mg/kg had no effects on gastric emptying or intestinal propulsion in fasted female Sprague Dawley rats.

Rat-Intravenous

Influence of Pantoprazole on Duodenogastric Saline Flow in Anesthetized Rats (GTR-31485).

Administration of pantoprazole by the intravenous route at doses of 0.38, 3.8, and 38 mg/kg had no effect on pyloric tone (as measured by saline flux from duodenum into stomach) in anesthetized rats.

Influence of I.V. Pantoprazole on Pancreatic and Bile Secretion in the Anesthetized Rat (GTR-31486).

Administration of pantoprazole by the intravenous route at doses of 3.8 and 11.5 mg/kg had no effects on volumes of pancreatic or bile secretions in anesthetized rats over a 3-hr monitoring period after dosing.

Neuropharmacology

Mouse and Rat-Oral and Intravenous

The Effect of Oral Pantoprazole on the Central Nervous System in Mice (GTR-31501).

Pantoprazole had no effect on CNS activity in male CD-1 mice following oral doses ≤100 mg/kg using the following tests: spontaneous locomotor activity, locomotor and exploratory activity, duration and threshold of hexobarbital-induced loss of the righting

reflex, maximal leptazol-induced convulsions, and leptazol seizure threshold, and anti-nociceptive activity. In the Irwin screen, no overt changes in behavior were observed at oral doses ≤ 100 mg/kg, but a dose of 1000 mg/kg produced CNS depression and hypothermia. It had no effect on CNS activity in female mice at oral doses ≤ 60 mg/kg using the following tests: locomotor activity (at night), coordination capacity using a rotarod, inhibition or potentiation of pentetrazole-induced seizures, anti-nociceptive activity, and duration of ethanol and hexobarbitone-induced sleeping times.

Influence of Oral or Intravenous Pantoprazole on Pupil Diameter of Female Mice (GTR-31481 and GTR-31480).

Oral administration of pantoprazole to female mice at doses of 100 and 300 mg/kg had no effects on pupil diameter (i.e., no miotic or mydriatic effects) over a 2-hr period after dosing. An oral dose of 1000 mg/kg produced slight pupil dilation; although, this effect was not statistically significant. Similarly, intravenous administration of pantoprazole to female mice at doses of 30 and 100 mg/kg had no effects on pupil diameter. These results suggest that pantoprazole had no significant effects on autonomic nervous system.

Influence of Pantoprazole on the Reaction Time of the Mouse in the Hot Plate Test (GTR-31494).

Administration of pantoprazole by the oral route at doses ranging from 5 to 60 mg/kg had no effect on pain induced by thermal sensation (i.e., anti-nociceptive activity) in female NMRI mice over a 2-hr period after dosing.

The Influence of Single and Repeated Administration of Pantoprazole on the Pentobarbital-Induced Lateral Position in Mice (GTR-31495).

The effects of single and repeated oral doses of pantoprazole on pentobarbital-induced sleeping time were assessed in female NMRI mice. In the single dose study, pantoprazole was administered at doses of 5 to 120 mg/kg, 60 min prior to pentobarbital treatment. In the repeat dose study, pantoprazole was administered at doses of 5 to 120 mg/kg/day for 3 day, and treatment with pentobarbital was given 60 min after the third dose. Single or repeat oral dose treatment with pantoprazole had no effect on pentobarbital-induced sleeping time in mice. These results suggest that pantoprazole did not possess CNS depressant or stimulant effects. Further, treatment with pantoprazole for 3 days did not effect drug metabolizing enzymes.

The Influence of Oral Pantoprazole on Sleeping Time After Hexobarbital in Mice (GTR-31496).

Administration of pantoprazole by the oral route at doses of 5, 20, 60, 80, and 120 mg/kg did not significantly alter hexobarbital (50 mg/kg)-induced sleeping time in female NMRI mice. This result suggested that pantoprazole neither stimulated nor inhibited the metabolism of hexobarbital.

The Influence of Oral Pantoprazole on the Duration of the Ethanol-Induced Lateral Position in Mice and Rats (GTR-31500 and GTR-31499).

Administration of pantoprazole by the oral route at doses of 0, 5, 20, and 60 mg/kg did not affect the duration of ethanol-induced hypnosis in female NMRI mice. Administration of pantoprazole by the oral route at doses of 0, 5, 20, 60, and 120 mg/kg did not affect the duration of ethanol-induced hypnosis in female Sprague Dawley rats.

Determination of Local Anesthetic Activity (Nerve Block) of Pantoprazole in Rats (GTR-31497).

Intravenous administration of pantoprazole (0.2 mL of a 2% solution) into the right thigh of female Sprague Dawley rats had no effect on locomotion on an inclined plate. Local injection did not effect sciatic nerve conduction, thus pantoprazole was considered to be devoid of local anesthetic activity.

Determination of Local Anesthetic Activity of Pantoprazole in Rats (Surface Anesthesia) (GTR-31498).

Topical instillation of pantoprazole (0.2 mL of a 2% solution) into the right eye of female Sprague Dawley rats had no effect on corneal reflex elicited by touching the cornea with a bristle. Pantoprazole did not cause local anesthesia of the cornea.

Cardiovascular/Respiratory Pharmacology

In Vitro

Investigations on the Possible Interaction of High Pantoprazole Concentrations with Smooth Muscle α_1- and Cardiac β_1-Adrenoreceptors (GTR-31506).

Pantoprazole (10^{-7}-3×10^{-5} M) had no effect on noradrenaline-induced contractions of rat vas deferens. Pantoprazole (10^{-5}-3×10^{-5} M) had no effect on isoprenaline-induced contractions of guinea pig right atrium. Thus, pantoprazole at concentrations $\leq 3 \times 10^{-5}$ M had no stimulatory or inhibitory effects with smooth muscle α_1- or cardiac β_1-adrenoreceptors in vitro.

Investigations of Pantoprazole in the Guinea-Pig Langendorff Heart (GTR-31479).

In the isolated, perfused Langendorff preparation of guinea pig heart, bolus injections of 10^{-8}-10^{-7} moles of pantoprazole had no significant effect on cardiac parameters (LVP, dP/dtmax, HR and CF). Doses $\geq 10^{-6}$ moles significantly depressed left ventricular pressure (-27% within 10-15 sec for 3×10^{-6} moles) and dP/dtmax (-47% in 10-15 sec for 3×10^{-6} moles) in this experiment, but returned to base line values within 1 min.

A rapid decrease in heart rate was observed at concentrations of 3×10^{-7} moles (-5%) to 3×10^{-6} moles (-19%); however, this effect was of short duration. Coronary blood flow was increased at pantoprazole concentrations of 3×10^{-7} (+14%) to 3×10^{-6} (+79%) M within 10 sec, but had dissipated within 3 min. Pantoprazole at doses $\geq 3 \times 10^{-7}$ mole transiently decreased heart rate and increased coronary blood flow. Pantoprazole at doses $\geq 10^{-6}$ mole transiently depressed left ventricular pressure and maximum rate of pressure rise.

In Vivo

Cat-Intravenous

The Effect of Intravenous Pantoprazole on Cardiovascular Autonomic Nervous System function in Anesthetized Cats (GTR-31475).

In anesthetized cats, intravenous infusion of pantoprazole at a dose of 30 mg/kg over a 15-min period, produced transient decreases in heart rate (20 beat min) and blood pressure (30 mm Hg); however, recovery occurred at 105 min after the end of the infusion. Pantoprazole had no effect on pressor responses and tachycardia elicited by bilateral carotid occlusion or I.V. norepinephrine (sympathetic) or depressor responses elicited by vagus nerve stimulation and I.V. acetylcholine (parasympathetic).

Hemodynamic Studies with Pantoprazole at a High Intravenous Dose in Anesthetized Cats (GTR-31476).

In anesthetized cats, intravenous infusion of pantoprazole at a dose of 30 mg/kg over a 15-min period, produced decreases in blood pressure (-13% compared to baseline) and total peripheral resistance (-24% compared to baseline). Blood pressure normalized after the end of the infusion; although, total peripheral resistance was decreased throughout the observation period. Stroke volume was increased during the infusion period and reached a peak effect of 31% over the baseline at 50 min after the end of the infusion. Similarly, aortic blood flow was increased was increased during the infusion period and reached a peak effect of 32% over the baseline at 60 min after the end of the infusion. Pantoprazole also caused vasodilation and increased cardiac output. There was no reflex tachycardia. Left ventricular stroke volume was presumed to increase due to enhanced venous return. Pantoprazole decreased total peripheral resistance leading to a fall in blood pressure. There were compensatory increases in stroke volume and aortic blood flow; however, heart rate was unchanged.

Hemodynamic Studies with Pantoprazole at an Intravenous Dose of 10 mg/kg in Anesthetized Cats (GTR-31477).

In anesthetized cats, intravenous infusion of pantoprazole at a dose of 10 mg/kg over a 15-min period, produced a decrease in total peripheral resistance with maximum reduction (-16%) occurring 15 min post-infusion. Stroke volume and aortic blood flow were increased during the infusion and reached peak effects of +12% and +16% over baseline at 50-55 min post-infusion, respectively. Pantoprazole also caused vasodilation and increased cardiac output. There was no reflex tachycardia. Left ventricular stroke volume was presumed to increase due to enhanced venous return. Pantoprazole decreased total

peripheral resistance leading to a fall in blood pressure. There were compensatory increases in stroke volume and aortic blood flow; however, heart rate was unchanged. Results are similar to those described in the previous study that used an intravenous dose of 30 mg/kg.

Dog-Intravenous

General Pharmacological Study of Pantoprazole (GTR-31452).

Pantoprazole administered by the intravenous route at doses of 1, 3, 10, or 30 mg/kg to female beagle dogs had no effect on respiratory rate, ECG, EEG, heart rate and blood pressure except, in high dose group where 2 out of 3 dogs had elevated heart rates (33 beats/min and 30-37 beats/min) at 15-30 min after drug administration. One of these dogs showed staggering gait for 10 min immediately following drug administration. Parameters were monitored for 30 min prior to drug administration and for 3 hr after drug administration.

Effects of Intravenous Infusion of Pantoprazole on Renal Function and Systemic Hemodynamics in Conscious Dogs (GTR-31478).

In hydropenic, female mongrel dogs (i.e., no food or water for 17-18 hr prior to test), pantoprazole, administered by intravenous infusion of 30 mg/kg over a 15-min period, had no effects on renal function as assessed by measurement of para-aminohippuric acid clearance, inulin clearance, electrolyte excretion, urine volume, pH, and osmolality. A significant decrease in blood pressure (-9 to -12% of baseline) occurred from 20 to 70 min after infusion of pantoprazole. Reflex tachycardia (29-54% of baseline) was observed in response to the decrease in blood pressure.

The Effects of Acute Intravenous Administration of Pantoprazole on Respiratory Function in the Anesthetized Dog (GTR-31487).

In anesthetized, male beagle dogs, pantoprazole, administered by the intravenous infusion at a dose of 30 mg/kg over a 15-min period, had no effect on respiratory function (i.e., respiratory flow, tidal volume, respiratory rate, transpulmonary pressure, dynamic compliance, or pulmonary resistance). Blood pressure decreased by 18% of baseline following infusion of pantoprazole as described in earlier studies with cats.

Other Studies

Effects on Body Temperature

Rat-Oral

Influence of Oral Pantoprazole on Body Temperature (GTR-31488).

Administration of pantoprazole by the oral route at doses of 5, 20, and 60 mg/kg to female Sprague Dawley rats had no effects on body temperature over a 5 hr monitoring period after dosing.

Effects on Locomotive Activity and on Muscle Strength and Coordination

Mouse-Oral

Influence of Pantoprazole on Motility in Mice (GTR-31489).

Administration of pantoprazole by the oral route at doses of 5, 20, and 60 mg/kg to female NMRI mice had no effects on spontaneous exploratory activity over a 15-hr period after dosing.

Influence of Oral Pantoprazole on the Coordination Capacity of the Mouse on the Rotarod (GTR-31490).

Administration of pantoprazole by the oral route at doses of 5, 20, and 60 mg/kg to female NMRI mice had no effects on grip strength or motor coordination using a rotating rod from 30 to 210 min after dosing.

Influence of Pantoprazole on Grip Strength of Mice (GTR-31492).

Administration of pantoprazole by the oral route at doses of 5, 20, and 60 mg/kg to female NMRI mice had no effects on grip strength from 30 to 210 min after dosing. This study suggests that pantoprazole did not cause CNS-mediated effects or peripheral effects on muscles involved in grip strength.

Influence of Oral Pantoprazole on Pentetrazole-Induced Seizures in Mice (GTR-31493).

Administration of pantoprazole by the oral route at doses of 5, 20, and 60 mg/kg to female NMRI mice did not inhibit or potentiate pentetrazole (45 or 30 mg/kg, respectively)-induced clonic seizures. This study suggests that pantoprazole did not exert convulsant or anticonvulsant activity. The incidence of lethality with pentetrazole was not altered by pantoprazole.

Mouse-Intravenous

Effects on Rotarod and Traction-Test in Female Mice (GTR-31491).

Administration of pantoprazole by the intravenous route at doses of 10, 30, or 100 mg/kg to female NMRI mice had no significant effect on rotarod and traction tests. This suggested lack of influence on central nervous function (coordination) and peripheral muscle.

In Vitro Interaction with Receptors in Isolated Tissues

Investigation on the Possible Interaction of Pantoprazole With B_2-Adrenoreceptors in Guinea Pig Trachea (GTR-31505).

Pantoprazole (10^{-7} - 3 x 10^{-6} M) had no effect on isoprenaline-induced relaxation of guinea pig tracheal chains in vitro. In this study, pantoprazole had no interactions with smooth muscle β_2-adrenoreceptors.

Investigations on the Possible Interaction of High Pantoprazole Concentration with Muscarinic M_3- and Histamine H_1-Receptors in Guinea Pig Isolated Ileum (GTR-31502).

Pantoprazole (10^{-8} - 10^{-4} M) had no effect on acetylcholine- and histamine-induced contractions of isolated guinea pig ileum. Thus pantoprazole at concentrations $\leq 10^{-4}$ M had no antagonistic activity toward muscarinic M_3 or histamine H_1 receptors.

Investigation on the Possible Interaction of Pantoprazole With α_{1B}-Adrenoreceptors in IsoGuinea Pig Spleen Strip (Report #107/95).

Pantoprazole (10^{-7} – 3 x 10^{-6} M) had no effect on norepinephrine-induced contractions of isolated guinea pig spleen strips. Pantoprazole at concentrations $\leq 3 \times 10^{-6}$ M had no effect on norepinephrine-induced stimulation of smooth muscle α_{1B}-adrenoreceptors.

Investigation on the Possible Interaction of Pantoprazole With Muscarinic M_1- and M_2- Receptors in Rabbit Vas Deferens (GTR-31503).

Pantoprazole (10^{-7} - 3 x 10^{-6} M) had no significant interaction with muscarinic M_1 and M_2-receptors in vas deferens tissue isolated from male rabbits.

Activity Against H. Pylori

Mouse-Oral

Potentiating Effects of Pantoprazole on the Effect of Various Antibiotics in the "Helicobacter Mouse Model" (GTR-31507).

In "Helicobacter mouse model", pantoprazole alone administered by the oral route at dose of 100 mg/kg t.i.d. (300 mg/kg/day) for 4 days had no effect on the status of Helicobacter infection. Amoxicillin (0.5 mg/kg t.i.d., oral), clarithromycin (0.5 mg/kg t.i.d., oral), and tetracycline (3 mg/kg t.i.d., oral) eliminated Helicobacter infection by 40%, 10%, and 55%, respectively. By combining pantoprazole with amoxicillin, clarithromycin, or tetracycline, Helicobacter elimination reached 100%, 90%, and 80%, respectively.

Additional Reports

Rat-Oral

Effect on Circadian Serum Gastrin Levels and Stomach Histology After Daily Oral Dosing of Pantoprazole in Rats (GTR-32366 and GTR-32369).

In two separate studies with female Wistar rats, the sponsor attempted to determine the effect on pantoprazole on circadian serum gastrin levels. In the first study, rats received pantoprazole by the oral route at doses of 1, 2.9, or 8.3 mg/kg/day for 28 days. In the second study, rats received pantoprazole by the oral route at doses of 1.04, 1.47, 2.01, or 3.03 mg/kg/day for 7 days. In both studies, pantoprazole was administered in the morning. Both studies were flawed in design. Pantoprazole should have been administered at different times of the day to assess differences in the gastrin response to drug treatment and its relationship to circadian rhythm.

Effect on Glucose Concentration in Rat Blood of a Single Oral Administration of Pantoprazole (GTR-32368).

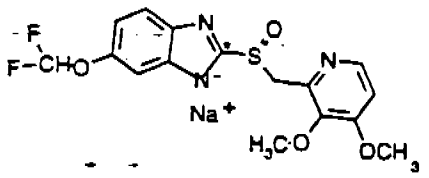
The effect of a single treatment with pantoprazole on serum glucose levels was assessed in fasting, male Sprague Dawley rats that received doses of 15, 30, or 60 mg/kg. Blood for determination of serum glucose levels was collected at 1 hr prior to treatment and at 2, 4, and 6 hr after treatment. Single treatment with pantoprazole at doses ≤ 60 mg/kg produced no biologically significant changes of serum glucose levels.

ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION

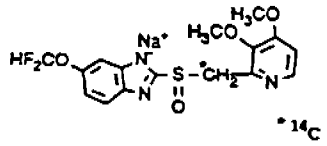
Several ADME studies were performed using radiolabeled pantoprazole. The ^{14}C label was located either in the benzimidazole ring (2-position) or in the methyl group attached to the pyridyl ring. Structures and positions of radiolabel are shown below.

2.1.2 [^{14}C]-Pantoprazole

Formula:



Chemical Name: Sodium-5-difluoromethoxy-2-(3,4-dimethoxy-2-pyridyl-methyl) sulfinyl-1H-2(^{14}C)-benzimidazole



[2-pyridylmethyl-^{14}C] 96022-Z

Absorption

Mouse

Pharmacokinetics of [^{14}C]Pantoprazole (25 and 150 mg/kg), [^{14}C]Omeprazole (70 and 140 mg/kg) and [^{14}C]Lansoprazole (75 and 600 mg/kg) in Male and Female Mice After a Single Intragastric Dose (GTR-27726).

Methods: The pharmacokinetics of pantoprazole, omeprazole, and lansoprazole were determined in B6C3 mice following administration by a single intragastric gavage. Radiolabeled pantoprazole, omeprazole, and lansoprazole were utilized in the present study. Pantoprazole was radiolabeled at the 2-position of the benzimidazole ring. Radiolabeled pantoprazole was administered at doses of 25 and 150 mg/kg. The vehicle was sterile water adjusted to pH 10 by addition of 0.1 M NaOH. Radiolabeled omeprazole was administered at doses of 70 and 140 mg/kg. Radiolabeled lansoprazole was administered at doses of 75 and 600 mg/kg. The vehicle for omeprazole and lansoprazole was 0.5% methyl cellulose/0.1% polysorbate 80 in 0.72% saline adjusted to pH 8 by addition of 0.5 M Na_2HPO_4. Blood samples were obtained by cardiac puncture at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8, and 24 hr after dosing and analyzed for plasma levels of total radioactivity and the parent compound. Four mice/sex were used for each time point. Plasma levels of radioactivity were determined with a ——— Plasma levels of pantoprazole, omeprazole, and lansoprazole were measured using a ——— method.

Results: Tables below show pharmacokinetic parameters for pantoprazole in terms of total radioactivity and the parent compound.

Following administration of pantoprazole, plasma C_{max} and AUC values for total radioactivity increased with ascending dose; although, increases were less than proportional to dose. Plasma C_{max} and AUC values for the parent compound (i.e., unchanged pantoprazole) increased with ascending dose; although, increases were greater than proportional to dose. Plasma C_{max} values for total radioactivity and the parent compound were greater in female mice than male mice. However, plasma AUC values for total radioactivity and the parent compound were generally similar between male and female mice. At a dose of 25 mg/kg, plasma AUC values for the parent compound represented 1 to 3% of total radioactivity for male and female mice, which suggested extensive metabolism. At a dose of 150 mg/kg, plasma AUC values for the parent compound presented 8.1 to 14.7% of the total radioactivity, which again suggested

extensive metabolism; although, less than observed at 25 mg/kg. These results suggested that pantoprazole underwent extensive first pass metabolism and rapid elimination. The greater than proportional increases for pantoprazole pharmacokinetic parameters may indicate saturable metabolism/elimination. The less than proportional increases for total radioactivity pharmacokinetic parameters may indicate saturable absorption. Studies with omeprazole and lansoprazole, similarly indicated that these compounds underwent extensive first pass metabolism and rapid elimination.

Pharmacokinetic parameters of plasma radioactivity and unchanged drug following intragastric administration of pantoprazole to male and female mice at doses of 25 and 150 mg/kg.

Parameters	Radioactivity				Unchanged Drug			
	25 mg/kg		150 mg/kg		25 mg/kg		150 mg/kg	
	Male	Female	Male	Female	Male	Female	Male	Female
AUC_{0-T}, μg equiv*hr/mL	32.4 (0-24 hr)	38.3 (0-24 hr)	103 (0-24 hr)	126 (0-24 hr)	0.438 (0-2hr)	1.20 (0-1hr)	15.1 (0-6hr)	10.2 (0-4hr)
$AUC_{0-\infty}$, μg equiv*hr/mL	-	-	106	152	-	-	16.3	11.1
C_{max}, μg equiv/mL	10.3	20.2	49.0	73.6	1.45	4.91	16.9	23.3
T_{max}, hr	6.0	0.25	0.5	0.25	0.25	0.25	0.25	0.25
T½, hr	-	-	5.3	11	-	-	2.3	1.7

Pharmacokinetics of Pantoprazole in CD-1 Mice After a Single Intragastric Dose (Report # GTR-27900).

Methods: Mice were given a single oral (gavage) dose of pantoprazole (710 mg/kg). Plasma sample were collected via cardiac puncture (4 mice/sex/time point were used) at 0, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 hr after drug administration. Levels of pantoprazole in the plasma samples were measured by

Results: Pantoprazole was absorbed rapidly in both sexes (T_{max} = 0.25 hr). The C_{max} and AUC_{0-24hr} values in males were 48.7 μg/ml and 63.7 μg*hr/mL, respectively, The C_{max} and AUC_{0-24hr} values in females were 28.0 μg/ml and 44.3 μg*hr/mL, respectively. In females, the t½ was 2.24 hr; however, in males, the t½ could not be calculated due to a secondary peak seen between 6 and 8 hours after drug administration.

Pharmacokinetics of ^{14}C-Pantoprazole, ^{14}C -Omeprazole and ^{14}C-Lansoprazole in Mice After Multiple Dosing (Report # GTR-27865).

Methods: Mice were given daily oral (gavage) doses of pantoprazole (150 mg/kg/day), omeprazole (140 mg/kg/day) or lansoprazole (600 mg/kg/day) for 6 consecutive days. On day 7, mice were given ^{14}C labeled drug (pantoprazole, omeprazole or lansoprazole) in a similar manner. The volume of administration was fixed at 10 mL/kg. Blood samples were

collected via cardiac puncture at 0, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 24 hr after the last dose and analyzed for total radioactivity and levels of parent drug (4 mice/sex/time point/treatment group were used). Radioactivity was determined by ——— and drug levels in plasma were measured by ———

Results: All three drugs were absorbed rapidly (T_{max} = 0.25 hr). Following pantoprazole administration, about 18% of the total radioactivity in plasma represented unchanged drug. Following administration of omeprazole or lansoprazole, approximately 1% of the total radioactivity in plasma represented unchanged drug, indicating that omeprazole and lansoprazole undergo more extensive first pass metabolism and faster elimination than pantoprazole.

Pharmacokinetic parameters of radioactivity and unchanged drug on day 7 following intragastric administration of pantoprazole to male and female mice at a dose of 150 mg/kg/day.

Parameter	Radioactivity		Unchanged Drug	
	Male	Female	Male	Female
C_{max}, µg equiv/mL	166.0	70.7	41.6	25.2
T_{max}, hr	0.25	0.25	0.25	0.25
AUC_{0-t}, µg equiv*hr/mL	0.5	0.25	18.8	9.62
$AUC_{0-\infty}$, µg equiv*hr/mL	107	79.6	-	-
T½, hr	3.2	4.6	-	-

Rat

Pharmacokinetic Studies in Male Rats Administered Single Oral Doses of 50, 300, 600 or 1200 mg/kg (GTR-31547).

Methods: Groups of male Sprague Dawley rats (6/group) were administered pantoprazole by oral gavage at a single dose of 50, 300, 600 or 1200 mg/kg. The volume of administration was fixed at 10 mL/kg and the drug solution pH was adjusted to 10.6 before administration. Blood samples were collected from tail vein at pre-test, 0.25, 0.5, 1, 2, 3, 4, 6, 8 and 24 hr after drug administration. Plasma pantoprazole levels were measured with a ———. Various pharmacokinetic parameters were calculated.

Results: Pantoprazole was absorbed rapidly (T_{max} = 0.25-0.33 hr). Plasma levels increased with increasing dosages, but increases were not proportional to dose. Hence, kinetics were non-linear. Half-lives (t½) increased with ascending dosages (0.8, 2.2, 5.2 and 6.7 hr at 50, 300, 600, and 1200 mg/kg, respectively). This non-linear kinetics of pantoprazole could be due to reduced absorption at higher dose levels (i.e., dissolution rate limited absorption) increased first-pass metabolism of pantoprazole, or increased volume of distribution due to increased unbound drug in plasma. Increased levels of unbound drug in plasma may also account for increased t½ values at higher dosages.

Mean pharmacokinetic parameters of pantoprazole in male rats administered single oral doses of 50 - 1200 mg/kg

Pharmacokinetic parameter	Dose administered (mg/kg)			
	50	300	600	1200
C_{max} (µg/ml)	26.033	62.394	77.422	112.222
T_{max} (hours)	0.33	0.25	0.29	0.25
AUC_{0-t} (µg.h/ml)	36.3	184.2	362.2	453.7
AUC (µg.h/ml)	36.5	191.7	380.9	519.3
k_e (hours^{-1})	0.9204	0.3149	0.1335	0.1029
t½ (hours)	0.8[a]	2.2[a]	5.2[a]	6.7[a]

[a] Calculated as ln2/mean k_e

Pharmacokinetics of —— 96022 in Rats Following Single and Multiple Oral Dose (5, 50 or 300 mg/kg) (GTR-31322).

Methods: Groups of rats (3/sex/group) were given pantoprazole —— 96022) by oral gavage at doses of 5, 50 or 300 mg/kg/day (expressed as free acid) for 30 days. The volume of administration was 10 mL/kg. Blood samples were collected from the lateral tail vein at 15, 30, 60 min. and 2, 4, 5, 6, 8, 10 and 12 hours after drug administration on days 1 and 30 of the study. In addition, blood samples were also collected just prior to drug administration on day 30 of the study. The levels of pantoprazole and its thiol metabolite —— 97165) were measured in serum samples by ———— (limit of detection ———— Various pharmacokinetic parameters were also calculated.

Results: Systemic exposure to pantoprazole or its thiol metabolite (——97165) on days 1 or 30 did not differ significantly. Pantoprazole was rapidly absorbed (T_{max} = 15 min), and levels increased with increasing dosage. The apparent T½ for pantoprazole at 5 mg/kg/day ranged from —— min. Serum levels of —— 97165 (thiol metabolite) also increased as the pantoprazole dose was increased from 50 to 300 mg/kg/day. At 5 mg/kg/day, negligible levels of —— 97165 were detected in the serum samples. There was no evidence of accumulation of drug or its metabolite in this study.

Serum pharmacokinetic parameters for unchanged drug and the thiol metabolite —— 97165) on days 1 and 30 in rats following oral treatment with pantoprazole at doses of 5, 50, and 300 mg/kg/day.

Dose mg/kg/day	Unchanged Drug						Thiol Metabolite —— 97165)					
	Day 1			Day 30			Day 1			Day 30		
	T_{max}	C_{max}	AUC	T_{max}	C_{max}	AUC	T_{max}	C_{max}	AUC	T_{max}	C_{max}	AUC
5	15	1.941	97.6	15	2.122	15	-	-	-	-	-	-
50	15	25.27	207.7	15	21.72	55.23	198	0.524	180.3	61	0.627	154.9
300	15	54.04	8683.4	15	55.23	12753	420	2.447	974.7	720	2.941	1230.1

T_{max}, min; C_{max}, µg/mL; and AUC_{0-T}, µg*min/mL

Detection of the Thiol Metabolite 97165) in Rat Plasma and Serum Following Single Oral Administration of Pantoprazole at Doses of 5, 50, and 300 mg/kg (GTR-31324).

Methods: Plasma and serum levels of the thiol metabolite of pantoprazole 97165) were measured in rats following oral administration of pantoprazole at doses of 5, 50, and 300 mg/kg. There was 1 rat/sex/dose. Rats were sacrificed as follows: 50 mg/kg, 1 hr after dosing; 0 and 50 mg/kg, 3 hr after dosing; and 300 mg/kg, 5 hr after dosing. Serum and plasma were prepared from blood samples collected after sacrifice. Serum and plasma levels of 97165 were measured by 97165 could be detected in rat plasma or serum over the range of μg/mL.

Results: 97165 was detected in plasma or serum samples in rats that received pantoprazole at oral doses ≥ 50 mg/kg.

Absorption and Bioavailability of Pantoprazole, Omeprazole, and Lansoprazole in the Rat After Administration Following a Single Intravenous or Oral Dose and Repeated Oral Dosing for 7 Days (GTR-31305).

Methods: The extent of absorption and absolute bioavailability of pantoprazole, omeprazole, and lansoprazole were examined in male Sprague Dawley rats following a single intravenous or oral administration of each compound and repeated oral administration of each compound for 7 days. In the repeat oral dose studies, doses were selected that matched high doses used in respective 2-year carcinogenicity studies. Each group consisted of six male rats. Rats received a single intravenous administration of each compound containing ^{14}C-radiolabel at a dose of 5 mg/kg. Blood samples were collected at 0.083, 0.25, 0.5, 1, 2, 3, 4, 6, and 24 hr after intravenous dosing. Rats received a single oral administration of each compound containing ^{14}C-radiolabel at a dose of 5 mg/kg. Blood samples were collected at 0.25, 0.5, 1, 2, 3, 4, 6, and 24 hr after oral dosing. Pantoprazole was administered to rats by oral gavage at doses of 50 and 200 mg/kg/day for 7 days. Omeprazole was administered to rats by oral gavage at doses of 50 and 141 mg/kg/day for 7 days. Lansoprazole was administered to rats by oral gavage at a dose of 50 mg/kg/day for 7 days. For repeat oral dose studies with pantoprazole, omeprazole, and lansoprazole, ^{14}C-radiolabeled drug was administered on days 1 and 7. On day 1, blood samples were collected at 0.25, 0.5, 1, 2, 4, 8, and 24 hr after dosing. On day 7, blood samples were collected at 0, 0.25, 0.5, 1, 2, 4, 8, and 24 after dosing. Unlabeled drug was administered on days 2 through 6. For oral or intravenous administration of pantoprazole, the drug was dissolved in water and adjusted to pH 10. For oral administration of omeprazole or lansoprazole, the test substance was suspended in 0.5% methylcellulose containing 0.72% NaCl and adjusted to pH 8.0 with 0.2% $NaHCO_3$. For intravenous administration of omeprazole or lansoprazole, the drug was dissolved in 40% PEG 400 in water and adjusted to a clear solution with NaOH. Stomach (divided into 3 sections), liver (divided into 3 sections), thyroid gland. and two hind leg femurs were collected at the end of toxicokinetic studies for determination of radioactive content. Radioactivity was measured by Plasma levels of the parent drug were determined by