In a 30-day oral toxicity study, beagle dogs received pantoprazole at doses of 0, 7.5, 15, 30, and 100 mg/kg/day. There were 5 dogs/sex/group. Two dogs/sex/group were sacrificed after 5 days and examined specifically for pulmonary changes. Remaining dogs were sacrificed after the 30-day treatment period. It appears that the dose of 15 mg/kg/day could be considered a tolerated dose given that stomach changes, described below, were most likely a result of the pharmacological action of the drug. Higher protein concentrations were observed in the lung lavage fluid from male dogs at 100 mg/kg/day for 5 days, but no such changes were detected after 30 days of dosing. Alveolar foamy macrophage were detected in the 100 mg/kg/day group on day 5, but no such changes were noted on day 30. One dog at 30 mg/kg/day for 5 days had alveolar hemorrhage; however, a similar change was observed for a control female on day 30. Following treatment for 30 days, parietal cell vacuolation in the stomach was detected at doses ≥15 mg/kg/day. Based upon lung lavage content of protein and foamy alveolar macrophages, lung injury appears to be most severe 3 to 5 days after the start of treatment, with resolution (i.e., adaptation) of changes occurring with continued treatment. Plasma C_{max} and AUC values for pantoprazole on days 1, 5, and 30 in male and female dogs generally increased in a manner proportional to increasing dose (i.e., linear toxicokinetics). Half-lives of plasma pantoprazole were generally increased in male and female dogs that received a dose of 100 mg/kg/day. Slower absorption at this dose may have contributed to the longer rate of elimination. Bioavailability of pantoprazole at oral doses of 7.5, 15, 30, and 100 mg/kg/day was generally greater in male dogs than female dogs; although, no gender-dependent differences in plasma C_{max} and AUC values were evident. Bioavailability values were probably only valid at the lower doses of 7.5 and 15 mg/kg/day (Males: 70.6 and 96.3%; Females: 58.0 and 51.1%) as bioavailability values in male dogs at doses of 30 and 100 mg/kg/day exceeded 100%.

In a 6-month oral toxicity study, beagle dogs received pantoprazole at doses of 0, 5, 15, 45, and 90 mg/kg/day. Additional dogs were included in the high dose groups for a 4-week recovery period following treatment. The recovery portion of the study was flawed due to a lack of a corresponding control group. In order to minimize lung toxicity at doses of 45 and 90 mg/kg/day that had been observed in earlier studies, doses were elevated in an incremental fashion. When the final dose was reached, the 6-month treatment period was started. Due to clinical signs of toxicity observed at doses of 45 and 90 mg/kg/day, dosages were reduced to 30 and 60 mg/kg/day, respectively. Ataxia, vomiting, tremor and loss of appetite were observed in the 90/60 mg/kg/day group and loss of appetite and tremor were observed in the 45/30 mg/kg/day group before the dosing was reduced. Increased serum gastrin levels were found in all treated male and female dogs; however, due to the large standard deviations and small number of animals used, significant increases ($p \leq 0.05$) were only observed for the female 5, 45/30, and 90/60 mg/kg/day groups. Increased cholesterol and triglyceride levels were observed in the 45/30 and 90/60 mg/kg/day groups. The stomach and liver were the target organs of toxicity. Inflammatory cell infiltrate in the cardiac and fundic region occurred at doses ≥15 mg/kg/day. Dilated crypts were noted in the stomach, duodenum, cecum, colon and rectum at doses ≥15 mg/kg/day. Brown pigment accumulation was found in the liver of the 90/60 mg/kg/day group and was still present at end of recovery period. Inspissated bile was observed in all drug treated groups. At weeks 14 and 26, AUC values for pantoprazole and the sulfone metabolite increased in a manner generally proportional to increasing dose.

However, AUC values for pantoprazole and the sulfone metabolite on day 1 increased with ascending dose; although increases were greater than proportional to ascending dose. Non-linearity on day 1 may have been due a lack of steady state levels. The AUC value for 5 mg/kg/day on day 1 was significantly lower than that observed at weeks 14 and 26. The pantoprazole half-life on day 1 for the dose of 90 mg/kg/day was greater than that observed at lower doses. Slower drug absorption may have resulted in a longer rate of elimination or liver enzymes may have been saturated.

In a 1-year oral toxicity study, beagle dogs received pantoprazole (non-enteric coated tablets in capsules) at doses of 0, 2.5, 15.0 and 60 mg/kg/day. The highest tested dose was achieved by dose escalation. The dose of 2.5 mg/kg/day could be considered a tolerated dose given that stomach changes, described below, are likely due to the pharmacological action of the drug. One male dog at 60 mg/kg/day had drug-induced pulmonary edema, which was resolved by the 7th day of the study. One male dog at 15 mg/kg/day died on day 4 of the study due to drug-induced pulmonary edema. Histopathological findings for this dog included peribronchial and periarteriolar edema, dilation of lymphatics, eosinophilic material in the alveoli, foamy alveolar macrophages, alveolar hemorrhage, and alveolar neutrophil infiltrates. A thiourea-like metabolite of pantoprazole (—— 97165) is thought to be responsible for induction of pulmonary edema following administration of pantoprazole. A pantoprazole dose as low as 15 mg/kg/day had the capacity to induce pulmonary edema. Pulmonary edema appears to be transient and tolerance develops with multiple dosing and has no relation to the animal supplier. Final body weights on day 364 were suppressed by >10% for male and female treatment groups at doses ≥15 mg/kg/day. At the end of treatment period, serum cholesterol levels were increased at all dose levels. Serum triglyceride levels were increased for all male treatment groups. Serum gastrin levels were elevated in all male and female treatment groups. The stomach, thyroid gland, gall bladder, and lungs were the target organs of toxicity. Histopathological findings for the stomach at doses ≥2.5 mg/kg/day were as follows: increased height of fundic mucosa, increased fundic mucosal folding, dilation of fundic gland, cellular debris in lumen of dilated gland, and increased chromogranin-positive cells in the fundic region. Additional findings at doses ≥15 mg/kg/day included vacuolation of parietal cells (multifocal). Pantoprazole had no effect on density of glucagon-like immunoreactivity positive cells in the mucosa or on mucosal mast cells. For the thyroid gland, hypertrophy of the follicular cells was seen for male dogs at doses ≥15 mg/kg/day and female dogs at 60 mg/kg/day. For the gall-bladder, crypt dilation was observed for all female treatment groups and one male dog at 15 mg/kg/day.

In a 4-week oral dose range finding toxicity study, the effects of pantoprazole on two different strains of mice (i.e., CD1 and B6C3F1) were examined. Mice received pantoprazole by oral gavage at doses of 0, 1, and 150 mg/kg/day. Groups of mice that received the vehicle or 150 mg/kg/day during the treatment period were allowed to enter a 4-week recovery period. At the end of the treatment or recovery periods, histopathological evaluation was confined to the liver, stomach, thyroid and lungs. No significant toxicities were identified for either mouse strain in this study. The target organs of toxicity were the stomach and liver. Serum gastrin levels and absolute stomach weights

were increased at 150 mg/kg/day for both strains. Histopathological examination of gastric fundus revealed parietal cell degeneration for CD1 mice at 150 mg/kg/day and B6C3F1 mice at 1 and 150 mg/kg/day, glandular dilation for CD1 mice at 1 and 150 mg/kg/day and B6C3F1 mice at 150 mg/kg/day, chief cell hyperplasia at 150 mg/kg/day in both strains, and parietal cell hyperplasia for CD1 mice at 1 and 150 mg/kg/day and B6C3F1 mice at 150 mg/kg/day. Changes in the stomach could be attributed to the pharmacological properties of pantoprazole. For the liver, eosinophilic cell swelling and/or vacuolization were observed for CD1 mice at 150 mg/kg/day and B6C3F1 mice at 1 and 150 mg/kg/day. At the end of 4 weeks of recovery period, histopathological abnormalities in the control and treated mice were comparable. The sponsor selected B6C3F1 strain of mice for repeat dose-range studies.

In a 4-week oral dose range finding toxicity study, female B6C3F1 mice received pantoprazole at doses of 5, 200, and 500 mg/kg/day. The sponsor identified this study as a dose range finding study for mouse carcinogenicity study with pantoprazole. At the end of the treatment period, histopathological evaluation was confined to the liver, lung, stomach and thyroid. Treatment-related mortality occurred at 500 mg/kg/day. Serum gastrin levels and stomach weights were increased at 200 and 500 mg/kg/day. The target organs of toxicity were the stomach and liver. Histopathological examination of gastric fundus revealed mucosal thickening at 200 and 500 mg/kg/day, parietal cell degeneration at 200 and 500 mg/kg/day, glandular dilation at all doses, parietal cell hyperplasia at all doses, chief cell atrophy at 500 mg/kg/day, yellow secretion at all doses, and submucosal edema at 500 mg/kg/day. In addition, hyperkeratosis in the forestomach and hyperplasia of the gastric antrum were observed at 200 and 500 mg/kg/day. Squamous cell metaplasia was evident in 1 of 5 mice at 500 mg/kg/day. For the liver, centrilobular hypertrophy was seen at all doses, and 1 of 7 mice at 500 mg/kg/day had hepatic necrosis. In this study, the maximum tolerated dose was not identified. The dose of 200 mg/kg/day produced only pharmacodynamic effects (i.e., changes in the stomach and increased serum gastrin levels) along with liver hypertrophy without hepatocellular necrosis.

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

In a 2-year carcinogenicity study, B6C3F$_1$ mice received pantoprazole by oral gavage at doses of 5, 25, and 150 mg/kg/day. Two additional groups were also included in the carcinogenicity study, one group was given vehicle (distilled water at pH 10.4) and the other group was used as an untreated cage control. At study termination, the survival rate for male mice at 150 mg/kg/day was reduced to 50% as compared to 84% for the cage control and 82% for the vehicle-control. Survival rate for female mice at 150 mg/kg/day was reduced to 62% as compared to 88% for the vehicle-control. There were no treatment-related effects on final body weights or food consumption. With regard to non-neoplastic histological findings, the target organs of toxicity were the stomach, liver, heart, gall bladder, and kidneys. For the stomach, a dose-dependent increase in the incidence of hyperplasia of the fundic region was found for both male and female mice. Dose-related increases in the incidence of focal and chain Grimelius Positive Cells (GPC) were found in male treatment groups. Submucosal growth was observed for male rats at 150 mg/kg/day. An increased incidence of focal, chain, and micronodule GPC were found for female mice at 150 mg/kg/day. For the liver, statistically significant increases in the incidence of Kupffer cell proliferation, patchy necrosis, fatty changes, and single cell necrosis were found for male and female mice at 150 mg/kg/day. Centrilobular necrosis was found for male mice at 25 and 150 mg/kg/day. An increased incidence of hepatocyte hyperplasia was observed for female mice at 150 mg/kg/day. For the heart, an increased incidence of distended chambers was found for male and female mice at 150 mg/kg/day. For the gall bladder, an increased incidence of distension was found for male mice at 150 mg/kg/day. For the kidney, an increased incidence of tubular dilation was found for male mice at 150 mg/kg/day. Additionally, 1 male mouse at 150 mg/kg/day was observed with osseous metaplasia in the kidney. For neoplastic findings, statistically significant increases in the incidence of hepatocellular adenomas ($p = 0.0257$) and carcinomas ($p = 0.0004$) were found for female mice at 150 mg/kg/day. The combined incidence of hepatocellular adenomas and carcinomas were significantly increased for female mice at 150 mg/kg/day. The combined incidence of liver tumors (adenomas + carcinomas) in female mice that received pantoprazole at 150 mg/kg/day exceeded incidences reported in the sponsor's historical control data (mean = 7.6% with a range of 6-8.2%) and published literature (Haseman et al. Journal of the National Cancer Institute 75: 975-984, 1985, mean = 8.3% with a range of 0-20%; NTP Historical Controls, mean = 5% with a range of range 0-15%; Maronpot et al., Arch. Toxicol. Suppl. 10: 10-26, 1987). The mean time to liver tumor (adenomas and/or carcinomas) was not affected by the treatment. Thus, hepatocellular adenomas and carcinomas found in female mice at 150 mg/kg/day were induced by pantoprazole treatment.

In support of the 2-year carcinogenicity study with B6C3F1 mice, plasma toxicokinetic parameters for unchanged pantoprazole were determined after a single dose (study LM0215) and after the last dose following two years (days 730-758) of continuous daily dosing (study KM8929, batch 399175). Serum AUC values for pantoprazole on day 1 and after 2 years were similar. However, C_{max} values after 2 years were 2 to 5 times higher than values observed on day 1. Serum AUC values on day 1 or after 2 years increased in a manner proportional to increasing dose. C_{max} values on day 1 increased in a manner approximately proportional to dose. However, after 2 years, C_{max} values increased with ascending dose; although, observed increases were less than proportional to dose.

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

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

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

Division's assessment of a positive carcinogenic potential for pantoprazole.

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

There were several neoplastic findings from the carcinogenicity study with pantoprazole in rats that differ significantly from carcinogenicity studies with other proton pump inhibitors (i.e., omeprazole and lansoprazole) in rats. For the stomach, neuroendocrine cell tumors (benign + malignant) have been observed in the fundus with all three agents. These tumors are thought to result from a hypergastrinemia produced by the pharmacological action of these agents; however, no elevation of serum gastrin levels were demonstrated in a 30-day study with pantoprazole doses of 0.5 or 1 mg/kg/day or in the 6-month toxicity study at a pantoprazole dose of 0.8 mg/kg/day, yet a

malignant neuroendocrine cell tumor was observed at 0.5 mg/kg/day in the carcinogenicity study. Additional neoplastic changes were observed in the stomach from pantoprazole-treated rats that have not been found with omeprazole or lansoprazole. These changes included: squamous cell carcinomas and papillomas in the forestomach; and rare tumors observed in the gastric glandular mucosa including chief cell adenocarcinoma in the fundus of one female, adenomatous polyps in the fundus of two males and one female, and adenocarcinoma in the pyloric region in one male. Additionally, neuroendocrine cell tumors were found in the liver of one animal at each pantoprazole dose level without identification of primary site (i.e., suggesting metastasis). Pantoprazole produced hepatocellular adenomas and carcinomas in rats. The sponsor has contended that pantoprazole is like phenobarbital and induces cytochrome P450 microsomal enzymes in rats, and concluded liver tumors were related to the promoter activity of the drug. Electron microscopic examination of livers from pantoprazole-treated rats has confirmed proliferation of the smooth endoplasmic reticulum; although, this drug is a very weak hepatic enzyme inducer and possesses only 0.025 times the potency of phenobarbital on a molar basis. Proton pump inhibitors, pantoprazole, omeprazole, and lansoprazole, are all weak hepatic enzyme inducer; however, in two-year carcinogenicity studies, only pantoprazole produced hepatocellular adenomas and carcinomas in the rat, which were statistically significant for both sexes. Thus, liver tumors observed in pantoprazole-treated rats cannot be explained solely on the basis of hepatic microsomal enzyme induction. Pantoprazole produced significant increases in the incidences of thyroid follicular cell adenomas and carcinomas in both male and female rats, which were not observed in 2-year carcinogenicity studies with omeprazole and lansoprazole. The sponsor has contended that thyroid tumors were generated in response to an imbalance of thyroid metabolism (i.e., Thyroid stimulating hormone-driven). TSH-driven thyroid follicular hypertrophy and hyperplasia can result from either direct inhibition of thyroid peroxidase (which incorporate iodine into T_4 and T_3) or indirectly through metabolism (i.e., glucuronide conjugation) and/or excretion (i.e., biliary), and receptor-mediated effects at hypothalamic and pituitary levels. In a 4-week study of thyroid function with Sprague Dawley rats, pantoprazole at 500 mg/kg/day decreased T_3 levels by 29-40% of the control and increased TSH levels by 2- to 3-fold; however, at 200 mg/kg/day, the highest dose used in the carcinogenicity study, there were no changes in T_3 or TSH levels. In a 2-week study with Sprague Dawley rats, pantoprazole at 200 mg/kg/day, the highest dose used in the carcinogenicity study with Sprague Dawley rats, had no effect on thyroid peroxidase activity and subsequent biosynthesis of thyroid hormones; although, uptake of iodine was enhanced as compared to the control following TSH stimulation. Following treatment of Sprague Dawley rats with either pantoprazole, lansoprazole, or omeprazole at doses of 5, 50, or 300 mg/kg/day for 1 week, significant induction of hepatic UDP-glucuronyl transferase (UDPGT) activity was observed with all three agents; however, the induction of UDPGT found with pantoprazole was smaller than that observed with either omeprazole or lansoprazole. Biliary excretion of [^{125}I]thyroxine (T_4) was significantly increased by the treatment of rats with all three agents; however, the increased biliary excretion of radiolabeled T_4 found with pantoprazole was much smaller than that observed with omeprazole or lansoprazole. Thus, the effects of pantoprazole on induction of hepatic UDPGT activity and thyroid hormone metabolism were smaller than those observed for omeprazole or lansoprazole; however, in 2-year carcinogenicity studies, thyroid tumor were only been observed with pantoprazole. Thus, thyroid tumor observed

in pantoprazole-treated rats cannot be explained by an imbalance of thyroid hormone metabolism (i.e., TSH-driven). In the 6-month oral toxicity study with Sprague Dawley rats, a hepatocellular adenoma was observed at 320 mg/kg/day. In the 12-month oral toxicity study with Sprague Dawley rats, a malignant neuroendocrine cell tumor was observed in gastric fundus at 5 mg/kg/day following a 9-month drug-free recovery period. Both in vitro and in vivo genotoxicity studies, described below, have shown that pantoprazole possesses mutagenic and clastogenic activity. These data demonstrate that pantoprazole possesses a carcinogenetic potential.

The effects of proton pump inhibitors, pantoprazole, omeprazole, and lansoprazole, on serum gastrin levels in female rats were examined following a 4-week treatment period. Rats were treated with pantoprazole at doses of 50 and 200 mg/kg/day, which were identical to doses used in the carcinogenicity study with Sprague Dawley rats. Rats were treated with omeprazole at doses of 45 and 138 mg/kg/day or lansoprazole at doses of 48 and 150 mg/kg/day. Omeprazole at 45 mg/kg/day and lansoprazole at 48 mg/kg/day were approximately equimolar to pantoprazole at 50 mg/kg/day. The high dose of each proton pump inhibitor used in the present study was identical to the high dose of each respective compound used in carcinogenicity studies with Sprague Dawley rats. Possible treatment-related deaths occurred for 1 rat in each of the high dose groups for pantoprazole and omeprazole. Gastrin levels were elevated on days 8/9 and 28/29 at 4 and 24 hr after dosing with pantoprazole, omeprazole, or lansoprazole; however, there were no findings to suggest dose response relationships. Levels at 4 hr after dosing were higher than levels at 24 hr after dosing. Values on days 8/9 and 28/29 were comparable. The stomach, liver, thyroid gland, and lungs were the target organs of toxicity. For the stomach in drug treatment groups, a dose-related increased incidence in the vacuolization of the fundic parietal cells was found. Chief cell hyperplasia was observed for animals that received omeprazole at 45 mg/kg/day, lansoprazole at 150 mg/kg/day, and pantoprazole at 200 mg/kg/day. The sponsor reported that semi-quantitative evaluation of enterochromaffin-like (ECL) cells in fundus found an increase of this cell type in all drug treatment groups. Dose-related increases in the number of these cells were found in omeprazole and lansoprazole groups, but the increase in pantoprazole groups was relatively flat (i.e., the incidence in groups that received pantoprazole at 50 or 200 mg/kg/day were relatively similar). A hyperplasia of the antral mucosa was observed for animals that received pantoprazole at 200 mg/kg/day, omeprazole at 138 mg/kg/day, and lansoprazole at 48 and 150 mg/kg/day. For the liver, an increased incidence of centrilobular hypertrophy was found in the high dose groups for all 3 compounds. For the thyroid gland, follicular cuboidal epithelium (i.e., activation of the thyroid gland) was observed for high dose groups that received pantoprazole or omeprazole, but not lansoprazole.

In a two-year carcinogenicity study, Fischer 344 rats received pantoprazole by oral gavage at doses of 5, 15, and 50 mg/kg/day. Two additional groups were also included in the carcinogenicity study, one group was given vehicle (distilled water pH 10.4) and the other group was used as an untreated cage control. No dose range finding studies were performed in order to select doses for this study with Fischer 344 rats. The sponsor contended that the high dose of 200 mg/kg/day, used in the carcinogenicity study with pantoprazole in Sprague Dawley rats, exceeded the maximum tolerated dose. Based upon

these results with Sprague Dawley rats, the sponsor selected doses of 5, 15, and 50 mg/kg/day for the carcinogenicity study with pantoprazole in Fischer rats. However, as noted above, dose selection for the carcinogenicity study with pantoprazole in Sprague Dawley rats was judged to be adequate. Furthermore, it is not scientifically valid to assess the MTD in one strain of rat and conduct carcinogenicity study in another strain of rat. In a 90-day dose range finding study with the thiol metabolite of pantoprazole (B8401-026/ 97165) in Fischer rats, the sponsor included a group that received pantoprazole at 200 mg/kg/day as a comparator. For Fischer rats that received pantoprazole at 200 mg/kg/day, there was no mortality or effects on body weight gain. Further, observed histopathological findings were of a minor nature and would not be expected to have any impact on survival. Thus, dose selection for the 2-year carcinogenicity study in Fischer rats was not appropriate. Treatment had no significant effect on mortality rates, final body weights, or food consumption. With regard to non-neoplastic findings, the target organs of toxicity were the stomach, liver, kidney, and adrenal glands. For the forestomach, there was a dose-related increase in the incidence of hyperplasia of the squamous epithelium in both male and female rats. For the fundus, there were increased incidences of eosinophilic chief cell hyperplasia, glandular ectasia, and basal fibrosis in both male and female rats; although, the incidences were not dose-related. There was an increased incidence of Grimelius positive cells focal hyperplasia and chain in the fundus for both male and female rats; although, dose response relationships were not evident. The incidence of micronodules of Grimelius positive cells was increased for both male and female rats at 15 and 50 mg/kg/day. The incidence of mucosal hyperplasia of antrum was increased for male and female rats at 15 and 50 mg/kg/day. For the liver, the incidence of pigment deposits was increased for male rats at 50 mg/kg/day and the incidence of spongiosis was increased in male rats at 15 and 50 mg/kg/day. The incidence of centrilobular hepatocellular hypertrophy was increased for all male and female treatment groups. For the kidney, a dose-related occurrence of interstitial nephritis was observed in male treatment groups; although, the overall incidence was low. Chronic progressive nephropathy was observed in all control and treatment group; although, the severity was increased in male rats at 50 mg/kg/day. For the adrenal glands, there was an increased incidence of pigment deposit for male rats at 15 and 50 mg/kg/day. For neoplastic findings, the incidence of benign + malignant neuroendocrine cell tumors (i.e., gastric carcinoids) was increased for male rats at 15 and 50 mg/kg/day and female rats at 5, 15, and 50 mg/kg/day. The highest tested dose of 50 mg/kg/day in this study was not the MTD. In spite of this major deficiency, pantoprazole treatment induced neuroendocrine cell tumors (benign + malignant) in male rats at 15 and 50 mg/kg/day and in female rats at 5, 15, and 50 mg/kg/day. This study is not very informative, due to major flaws in dose selection, however, it confirms some findings of the carcinogenicity study in Sprague Dawley rats.

Serum levels of pantoprazole and its sulfone metabolite were measured on days 1, 367, and 710 in Fischer rats that received pantoprazole at doses of 5, 15, and 50 mg/kg/day. The sulfone of pantoprazole is the main serum metabolite in the rat. Serum AUC values for pantoprazole were generally higher in female rats than male rats on days 1, 367, and 710. In contrast, serum AUC values for the sulfone metabolite were generally higher in male rats than female rats on days 1, 367, and 710. AUC values for pantoprazole on days 1, 367, and 710 increased in a dose proportional manner. AUC values on days 367 and 710 were relatively comparable; however, AUC values on day 1 were significantly lower. AUC values for the sulfone increased with ascending doses; however, increases were greater than proportional to dose.

The tumor promoting activity of pantoprazole was assessed in the stomach and forestomach of Sprague Dawley rats. This mechanistic study was intended to evaluate the potential tumor promoting activity of pantoprazole in combination with a strong initiating carcinogen, N-methyl-N-nitroso-guanidine (MNNG). The incidence of mortality was increased for treatment groups that received MNNG. The sponsor attributed high mortality in these groups to MNNG + oral gavage. Moderate to severe multifocal or diffuse squamous metaplasia of the non-squamous laryngeal epithelium was observed in treatment groups that received MNNG. Partial obstruction of the laryngeal lumen was observed in these animals and appeared to correlate with severe breathing sounds. Focal or multifocal aspiration pneumonia was observed with an increased incidence in treatment groups that received MNNG. It should be noted that esophageal lesions were most prevalent for the treatment group that received pantoprazole alone. Control animals received no treatment, which made it impossible to assess the deleterious effects of oral gavage alone. The glandular stomach was study target organ with regard to evaluating the tumor promoting activity of pantoprazole. The incidence of antral adenocarcinoma in the glandular stomach for female rats that received MNNG + pantoprazole was increased to 35% (7/20) as compared to 5% (1/20) for female rats that received MNNG + vehicle, suggesting that pantoprazole was acting as a tumor promoter. However, the incidence of antral adenocarcinoma for male rats that received MNNG ± pantoprazole was approximately equivalent [4/20 (20%) vs. 5/20 (25%)]. Significant histopathological findings were evident for the forestomach and glandular stomach. Squamous epithelial hyperplasia and hyperkeratosis in the forestomach were evident for treatment groups that received pantoprazole. Hyperplasia of the fundic and antral mucosa in the glandular stomach were evident for treatment groups that received pantoprazole. The increased incidence of antral adenocarcinoma in the glandular stomach for female rats that received MNNG + pantoprazole as compared to female rats that received MNNG + vehicle possibly suggests that pantoprazole possesses tumor promoting activity; however, incidences for corresponding male treatment groups were approximately equivalent suggesting this observation in female rats was possibly by chance and influenced by high mortality in the study.

The tumor promoting activity of pantoprazole was assessed in the liver and thyroid gland of Sprague Dawley rats. This mechanistic study was intended to evaluate the potential tumor promoting activity of pantoprazole in combination with a strong initiating carcinogen, N-nitroso-N-methylurea (NMU). The study protocol was based upon the experimental protocol described by Diwan et al. (Journal of the National Cancer Institute 75: 1099-1105, 1985. In the study conducted by the sponsor to assess the tumor promotional activity of pantoprazole, there was a high incidence of mortality related to technical errors associated with administration of pantoprazole by oral gavage; although, this was not observed with the vehicle of pantoprazole. Tumor incidences in thyroid gland were low and confined to one sex in the positive control group, NMU + phenobarbital, possibly due to high mortality rates in the study. Diwan et al. (JNCI 75: 1099-1105, 1985) reported a significantly higher yield of follicular cell adenomas at 52 weeks for both male and female Fischer rats. In the present study conducted by the sponsor, the positive control produced a negative response with regard to thyroid gland tumors and thus, the study could be assumed to have no validity with regard to the thyroid gland. The sponsor combined incidences of hepatocellular neoplasms and foci of cellular alterations for female rats to suggest that pantoprazole could be acting as a promoter. However, similar results were not obtained with corresponding male treatment groups. Diwan et al. (JNCI 75: 1099-1105) reported that for both male and female Fischer rats, which received phenobarbital for 52 weeks after NMU treatment, were observed with an increased area of hepatocellular foci of cellular alteration/cm^2. It should be noted that Diwan et al. (JNCI 75: 1099-1105) did not combine hepatocellular adenomas/carcinomas with foci of cellular alteration. Further, Diwan et al. (JNCI 75: 1099-1105) and Harada et al. (Toxicol Pathol. 17:579-593, 1989) have reported that there is no constant proportion between foci of cellular alteration and subsequent development of hepatic neoplasms. The increase of combined incidence of hepatocellular neoplasms and foci of cellular alterations for female rats that received NMU + pantoprazole possibly suggests that pantoprazole possesses tumor promoting activity; however, incidences for corresponding male treatment groups were approximately equivalent suggesting these observations in female rats occurred by chance and were influenced by high mortality in the study.

In an oral Segment I fertility and reproductive performance study, male Sprague Dawley rats received pantoprazole by gavage at doses of 0, 5, 50, and 500 mg/kg/day for 70 days prior to mating with untreated female rats. Pantoprazole at oral doses ≤500 mg/kg/day had no effect on fertility and reproductive performance in male rats. Prostration, ataxia, decreased motor activity, abdominal gait and/or abnormal reflex were observed in male rats at 500 mg/kg/day. Body weight gain was impaired by 12% for male rats at 500 mg/kg/day. Seminal vesicle weight was increased for male rats at 500 mg/kg/day. Testis and epididymis counts and histological change in testis or epididymides were normal. In the first mating trial, the fertility index (54-80%) was low for the control and all treatment groups. In a second mating trial after 112 days of treatment, fertility indexes ranged from 83 to 96% in the control and treatment groups. The mating index ranged from 92 to 100% for control and treatment groups in both trials.

In an oral Segment I fertility and reproductive performance study, female Sprague Dawley rats received pantoprazole by oral gavage at doses of 0, 50, 150, and 450 mg/kg/day from 14 days prior to mating and through the gestation and lactation periods. Pantoprazole at oral doses ≤450 mg/kg/day had no effect on fertility and reproductive performance in female rats. Body weight gain was impaired by 12% in female rats at 450 mg/kg/day. There were no treatment-related effects on mating or fertility indexes.

In an intravenous Segment II teratology study, pregnant female Sprague Dawley rats received pantoprazole at doses of 0, 1, 4, or 20 mg/kg/day from days 6 to 15 of gestation. Pantoprazole at intravenous doses ≤20 mg/kg/day had no teratogenic effects in rats. The number of corpora lutea, number of implantations, early and late resorptions, and mean fetal body weight were unaffected by treatment. There were no treatment-related external and visceral malformations or variations. There were no treatment-related skeletal malformations; however, delays in ossification were evident for fetuses from dams at 20 mg/kg/day.

In an oral Segment II teratology study, pregnant female Sprague Dawley rats received pantoprazole by gavage at doses of 0, 50, 150, and 450 mg/kg/day from days 6 to 15 of gestation. Pantoprazole at oral doses ≤ 450 mg/kg/day had no teratogenic effects in rats. Prostration, eating bedding material, and piloerection were observed for female rats at 450 mg/kg/day. Body weight gain was impaired by 12% for female rats at 450 mg/kg/day. There were no treatment-related effects on number of corpora lutea/dam, number of implanations/dam, post-implantation loss, live fetuses/dam, or fetal body weight. An increased pre-implantation loss was observed with dams at 450 mg/kg/day. There were no treatment-related external or visceral malformations or variations. There were no treatment-related skeletal malformations; however, there was a dose-dependent delay of ossification for fetal cranial bones.

In an oral Segment II teratology study, pregnant female Sprague Dawley rats received pantoprazole by the oral route at doses of 0, 5, 15, and 50 mg/kg/day from days 6 to 15 of gestation. This study was performed in order to identify an oral no effect dose for delay of ossification for fetal cranial bones that had been observed in earlier Segment II studies. Pantoprazole at doses ≤50 mg/kg/day produced no evidence of teratogenic effects. There was no evidence of maternal toxicity (i.e., decreased body weight or food consumption, clinical signs of toxicity) at doses ≤50 mg/kg/day. Skeletal examination of fetuses revealed that the dose of 5 mg/kg/day had no effect on ossification for bones in the skull. At doses of 15 and 50 mg/kg/day, there was evidence of incomplete ossification for bones in the skull; however, it should be noted that these effects were variations, which have no effect on survival.

In an intravenous Segment II teratology study, pregnant female rabbits received pantoprazole at doses of 0, 1.5, 5, and 15 mg/kg/day from days 6 to 18 of gestation. Pantoprazole at intravenous doses ≤15 mg/kg/day was not teratogenic in rabbits. No treatment-related clinical signs and mortality were seen during study period. The number of corpora lutea, the number of implants, pre- and post-implantation loss, mean fetal weights and sex ratio did not show any significant difference between the treated and control groups. No treatment-related abnormalities were seen in external, skeletal and visceral examinations in any group, except delayed dental growth was observed at 5 and 15 mg/kg/day.

In an oral Segment II teratology study, pregnant female rabbits received pantoprazole by intubation at doses of 0, 2.5, 10, and 40 mg/kg/day from days 6 to 18 of gestation. Pantoprazole at oral doses ≤40 mg/kg/day was not teratogenic in rabbits. Food consumption was reduced by 9.25% for dams at 40 mg/kg/day. The number of corpora lutea, the number of implants, pre- and post-implantation loss, mean fetal weights and sex ratio did not show any significant difference between the treated and control groups. No treatment-related abnormalities were seen in external, skeletal and visceral examinations in any group, except delayed dental growth was observed at 40 mg/kg/day.

In an oral Segment III perinatal and postnatal development study, pregnant female Sprague Dawley rats received pantoprazole by gavage at doses of 0, 1, 3 and 30 mg/kg/day from day 15 of gestation to day 21 after parturition. Pantoprazole at doses ≤30 mg/kg/day had no significant effects on perinatal and postnatal development in rats. Food consumption during lactation for dams at 30 mg/kg/day was reduced 7% as compared to the control group. No treatment-related effects were seen in the F_1 pups during the postnatal period except that body weight gain of pups at 30 mg/kg/day was significantly reduced by 19-22% during the lactation period as compared to control values. This retardation of body weight gain was still evident in male offspring until 12 weeks of age. At the end of 12 weeks, weights of male pups from the high dose group were about 8% lower than that observed in pups of the control group. Development and reproductive performance were comparable in all groups.

The genotoxic potential of pantoprazole was assessed with a number of in vitro and in vivo studies. In vitro studies included the bacterial reverse mutation assay, human lymphocyte chromosomal aberration assay, Chinese hamster ovary cell hypoxanthine guanine phosphoribosyl transferase (CHO/HGRPT) forward mutation assay, unscheduled DNA synthesis assay with rat hepatocytes, AS52/GPT mammalian cell-forward gene mutation assay, thymidine kinase mutation test with mouse lymphoma L5178Y cells, and malignant transformation assay with C3H M2-fibroblasts. In vivo studies included the mouse micronucleus assay, the rat bone marrow chromosomal aberration assay, measurement of DNA binding with rats; and ^{32}P-postlabeling experiment with hepatic liver DNA. In four separate tests, chromosomal aberration assays using human lymphocytes with pantoprazole produced positive responses. In the CHO/HGPRT forward mutation assay, pantoprazole produced a positive response in 2 of 3 tests. In the mouse

micronucleus test, doses of 177.5 and 710 mg/kg produced a positive response at the 24 hr sampling time. In a second mouse micronucleus test, doses ≤710 mg/kg at sampling times of 24 or 36 hr produced a negative response. In a covalent binding assay with rat liver DNA, pantoprazole produced a positive response. The covalent binding index was 1.6 for rats that received a 14-day pretreatment with 200 mg/kg/day pantoprazole followed by a single treatment with radiolabeled pantoprazole as compared to 0.70 for rats that received a 14-day pretreatment with vehicle followed by a single treatment with pantoprazole. This study clearly indicated that pantoprazole radioactivity could bind to rat liver DNA and pretreatment with pantoprazole for 14 days increased the covalent binding index by 2.3-fold. A ^{32}P-postlabeling experiment was performed with hepatic DNA obtained from female Sprague Dawley rats treated with pantoprazole by the oral route at a dose of 200 mg/kg/day for 4 weeks. DNA damage assessed by ^{32}P-postlabeling suggested that pantoprazole treatment led to the formation of a unique DNA adduct not observed in control samples. An "extra spot" was observed with pantoprazole samples in three different ——— systems that was not found in control samples. These results suggested that pantoprazole or one of its metabolites directly interacts with DNA to form an adduct. Quantition of DNA was unreliable; however, the ——— pattern clearly indicates that pantoprazole treatment lead to the formation of a unique adduct. No such results were obtained with omeprazole (200 or 600 mg/kg/day) or lansoprazole (200 or 1200 mg/kg/day). Pantoprazole was negative in the in vitro bacterial reverse mutation assay, the unscheduled DNA synthesis assay with rat hepatocytes, AS52/GPT mammalian cell-forward gene mutation assay, thymidine kinase mutation test with mouse lymphoma L5178Y cells, malignant transformation assay with C3H-Mouse M2-fibroblasts, and SHE cell transformation assay. Pantoprazole was negative in vivo with the bone marrow chromosomal aberration test using rats. Genotoxicity studies indicate that pantoprazole can produce chromosomal aberrations with human lymphocytes, induce forward mutations at the HGPRT locus in Chinese hamster ovary cells, bind with rat liver DNA, and form adduct(s) with rat liver DNA. Pantoprazole possesses mutagenic and clastogenic activity.

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

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

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

In early toxicity studies with pantoprazole in dogs, the development of a potentially fatal pulmonary toxicity was observed. To assess the potential pulmonary toxicity of pantoprazole, the sponsor conducted a number of studies with rats and dogs. Dogs appeared to be highly sensitive to pantoprazole-induced pulmonary toxicity, whereas rats were not. In a dose range finding toxicity study, beagle dogs received drug at intravenous doses of 0, 7.5, 15, 30, and 50 mg/kg/day for 5 days. At 50 mg/kg/day, death of one dog and moribund sacrifice of two other were attributed to pulmonary toxicity (i.e., fluid effusion into the pulmonary alveoli). Histopathological analysis of the lung for dogs at 50 mg/kg/day revealed areas of alveolar hemorrhage, eosinophilic material in alveoli (i.e., protein), and neutrophils in the alveoli. Areas of foamy alveolar macrophages were evident at doses ≥15 mg/kg/day. The no effect dose for pantoprazole-induced pulmonary toxicity in dogs appeared to be 7.5 mg/kg/day. In another study, electron microscopy studies revealed evidence of necrosis of a small proportion of alveolar capillary endothelial cells, in dogs treated with pantoprazole for 5 days by the oral route at 100 mg/kg/day or by the intravenous route at 50 mg/kg/day, which was considered indicative of vascular leakage with fluid effusion into the alveoli. The toxicokinetic relationship between pulmonary toxicity and systemic exposure to the thiol metabolite of pantoprazole (B8401-026/ —— 97165) was examined in beagle dogs that received either pantoprazole at intravenous doses of 0, 15, and 50 mg/kg/day (the high dose was reduced to 40 mg/kg/day on day 2) or the thiol metabolite at intravenous doses of 2.5, 5, and 15 mg/kg/day for 5 days. Protein content in the lung fluid was elevated for all treatment groups. Moderate vacuolation of macrophage cytoplasm, foamy alveolar macrophages, and increased lung water content were found with pantoprazole at 50/40 mg/kg/day and the thiol metabolite at 5 and 15 mg/kg/day. Study parameters indicate that the same processes were occurring following administration of either pantoprazole or its thiol metabolite and that a dose-responsive relationship existed with both compounds. Systemic exposure to the thiol metabolite was > 700 μg*min/mL in all dogs that had evidence of alveolar effusion. These finding seem to supports the concept that pantoprazole-induced pulmonary toxicity might be associated with the thiol metabolite (B8401-026/ —— 97165). The sponsor's analytical methodology to identify and quantify the thiol metabolite is highly questionable at the time of this review. It should be noted that the thiol metabolite is highly reactive and rapidly binds with cellular components.

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

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

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

Several local tolerance studies were performed with pantoprazole in rats, rabbits, and dogs and the thiol metabolite in rabbits. No differences in incidences or severity of necrosis or local signs of intolerance were found following intramuscular injection of either the placebo or pantoprazole to rats. No signs of local intolerance were observed with rabbits that received a single intravenous injection of a 0.4% pantoprazole solution; however, more extensive local reactions (i.e., discoloration, swelling, and scabs at the injection site) were observed with a 6% solution. Microscopic evaluation found hemorrhagic necrotizing tissue changes in the area around the central ear artery and clot formation (i.e., thrombus in organization or thrombotic residue) within the artery itself. These changes are presumed to occur due to occlusive vascular processes, which may have caused by the pH of solution at 9 to 11. The sponsor stated that the maximum therapeutic concentration for parenteral use should be 2.56%. A single intravenous, paravenous, or intraarterial injection of 0.4% pantoprazole (free acid) into the ear did not produce local irritation in rabbits (two studies). Pantoprazole and its thiol metabolite (B8401-026) had a low potential of dermal irritation in rabbits. There were no signs of local irritancy following intravenous and paravenous administration of pantoprazole to one male beagle dog.

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

In humans, pantoprazole enteric-coated tablets will be administered by the oral route for periods generally ranging from 4 to 8 weeks. Under some circumstances, the treatment period could potentially be as long as 16 weeks. The sponsor has conducted sufficient preclinical toxicology studies. Both in vitro and in vivo genotoxicity tests suggest that pantoprazole can bind with DNA and possesses mutagenic and clastogenic activity.

Further, pantoprazole in carcinogenicity studies with B6C3F1 mice, Sprague Dawley rats, and Fischer 344 rats was found to have a positive tumorigenic potential. As discussed earlier, tumor findings with pantoprazole in the carcinogenicity study with Sprague Dawley rats differ significantly from findings with omeprazole and lansoprazole. For the stomach, neuroendocrine cell tumors (benign + malignant) have been observed in the fundus with all three drugs. These tumors are thought to result from a hypergastrinemia produced by the pharmacological action of these agents; although, no elevation of gastrin levels was demonstrated with pantoprazole at a dose level of 0.5 mg/kg/day, yet a malignant neuroendocrine tumor was observed. There were additional neoplastic changes observed in the stomach from pantoprazole-treated rats that have not been found with omeprazole or lansoprazole. These changes included squamous cell carcinomas and papillomas in the forestomach, a chief cell adenocarcinoma in the fundus, adenomatous polyps in the fundus, and an adenocarcinoma in the pyloric region. Neuroendocrine cell tumors were found in the liver, lymph nodes, and multiple organs, which indicated the occurrence of tumor metastases. Pantoprazole produced hepatocellular adenomas and carcinomas in rats, which cannot be explained solely on the basis of hepatic microsomal enzyme induction. Pantoprazole produced significant increases in the incidences of thyroid follicular cell adenomas and carcinomas, which were not observed in 2-year carcinogenicity studies with omeprazole and lansoprazole, and cannot be explained by an imbalance of thyroid hormone metabolism. In the 6-month oral toxicity study with Sprague Dawley rats, a hepatocellular adenoma was observed at 320 mg/kg/day. In the 12-month oral toxicity study with Sprague Dawley rats, a malignant neuroendocrine cell tumor was observed in gastric fundus at 5 mg/kg/day following a 9-month drug-free recovery period. These data demonstrate that pantoprazole possesses a carcinogenetic potential. From a preclinical standpoint, the application is not recommended for approval.

The label is not according to 21 CFR, 201.50 Subpart B (April 1, 1998), and changes in text as outlined in the review portion are needed.

APPEARS THIS WAY
ON ORIGINAL

RECOMMENDATION:

From a preclinical standpoint, the application is not recommended for approval. The label is not according to 21 CFR, 201.50 Subpart B (April 1, 1998), and changes in text as outlined in the review portion are needed.

/S/
Timothy W. Robison, Ph.D.

4-13-99
Date

Attachments:

Appendix 1A: Mouse Carcinogenicity Study, Histopathology - Tumor Data – Pages 343-348
Appendix 1B: Mouse Carcinogenicity Study, Histopathology - Non-Neoplastic Lesion Data – Pages 349-362
Appendix 2A: Sprague Dawley Rat Carcinogenicity Study, Histopathology - Tumor Data – Pages 363-379
Appendix 2B: Sprague Dawley Rat Carcinogenicity Study, Histopathology - Non-neoplastic Lesion Data – Pages 380-412
Appendix 3A: Fischer 344 Rat Carcinogenicity Study, Histopathology - Tumor Data – Pages 413-426
Appendix 3B: Fischer 344 Rat Carcinogenicity Study, Histopathology - Non-neoplastic Lesion Data – Pages 427-465

cc:
Orig NDA 20,987
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison
HFD-345/Dr. Viswanathan

R/D Init.: J. Choudary 3/15/99

TWR/hw/4/1/99 & 4/13/99

(1) Concur

(2) A Team Leader Memorandum on Labeling will follow.

/S/

4/20/99

APPENDIX 1A

Mouse Carcinogenicity Study
Histopathology - Tumor Data

Pages 343 - 348

APPEARS THIS WAY
ON ORIGINAL

NDA 20,987
Page 344

PATHOLOGY REPORT 42/92 PAGE H : 57/ 937
SUMMARY TABLES STUDY NO. : KM8929

TEST ARTICLE : B8610-023 PATHOL. NO.: 92003
TEST SYSTEM : MOUSE, CARCINOGENICITY STUDY, DATE : 25-NOV-92
SPONSOR : BYK GULDEN, HAMBURG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX IN %
STATUS AT NECROPSY: KO, INCL. +

SEX :					MALE
DOSE GROUP:	K1	K2	N	M	H
NO.ANIMALS:	50	50	50	50	50
SEMINAL VESICLES	50	50	50	50	50
- LEIOMYOSARCOMA		2.0			
TESTES	50	50	50	50	50
- LEYDIG CELL TUMOR		2.0		4.0	2.0
KIDNEYS	50	50	50	50	50
- METASTATIC CARCINOMA			2.0		
ADRENAL GLANDS	50	50	50	50	50
- PHEOCHROMOCYTOMA				2.0	
- CORTICAL ADENOMA			2.0	2.0	
- METASTATIC CARCINOMA			2.0		
PANCREAS	50	50	50	50	49
- ISLET CELL ADENOMA	2.0	4.0			
SPLEEN	50	50	50	50	50
- HEMANGIOSARCOMA		4.0	4.0	2.0	
LIVER	50	50	50	50	50
- CARCINOMA, HEPATOC.	18.0	24.0	24.0	24.0	26.0
- ADENOMA, HEPATOC.	20.0	22.0	14.0	26.0	12.0
- HEMANGIOMA	4.0	2.0	2.0	2.0	
- HEMANGIOSARCOMA	2.0			2.0	
HEMOLYMPHORET. SYS.	50	50	50	50	50
- MALIGNANT LYMPHOMA	12.0	8.0	8.0	8.0	14.0
- MYELOID LEUKEMIA		2.0	2.0		
SKIN	50	50	49	49	50
- HEMANGIOSARCOMA	2.0				
- SARCOMA NOS		2.0			
MAMMARY GLAND AREA	50	50	49	49	50
- HEMANGIOMA	2.0				

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TEST ARTICLE : B8610-023 PATHOL. NO.: 92003
TEST SYSTEM : MOUSE, CARCINOGENICITY STUDY, DATE : 25-NOV-92
SPONSOR : BYK GULDEN, HAMBURG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX IN %
STATUS AT NECROPSY: KO, INCL. +

SEX :					MALE
DOSE GROUP:	K1	K2	M	H	
NO.ANIMALS:	50	50	50	50	50
SKELETAL MUSCLE	50	50	50	49	50
- HEMANGIOMA	2.0				
- SARCOMA		2.0			
- METASTATIC CARCINOMA			2.0		
THYROID GLAND	50	49	50	50	50
- FOLLICULAR ADENOMA	4.0			6.0	
HARDERIAN GLANDS	49	50	49	50	50
- ADENOMA	10.2	10.0	6.1	12.0	8.0
PITUITARY GLAND	49	49	46	50	49
- ADENOMA	2.0				
LUNGS	50	50	50	50	50
- BRONCH./ALV. TUMOR	26.0	28.0	28.0	22.0	16.0
- METASTATIC CARCINOMA	2.0		6.0	4.0	2.0
- METASTATIC SARCOMA			2.0		
STOMACH	50	50	50	50	50
- PAPILLOMA	2.0				
- ADENOMATOUS POLYP	2.0				
LARGE INTESTINE	50	50	50	50	50
- LEIOMYOSARCOMA		2.0			
BODY CAVITIES		1	2	1	2
- HEMANGIOSARCOMA			n<10		
ADIPOSE TISSUE	2	2	1	2	4
- HEMANGIOSARCOMA				n<10	
- LIPOMA	n<10				

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TEST ARTICLE : B8610-023 PATHOL. NO.: 92003
TEST SYSTEM : MOUSE, CARCINOGENICITY STUDY, DATE : 25-NOV-92
SPONSOR : BYK GULDEN, HAMBURG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX IN %
STATUS AT NECROPSY: KO, INCL. +

SEX :					FEMALE
DOSE GROUP:	K1	K2	N	M	H
NO.ANIMALS:	50	50	50	50	50
PAROTID GLANDS	50	50	50	50	50
- HEMANGIOMA				2.0	
UTERUS	50	50	50	50	50
- HEMANGIOMA	2.0		2.0	2.0	
- POLYP	2.0	4.0		4.0	
- LEIOMYOMA		2.0	2.0	2.0	
- LEIOMYOSARCOMA		2.0			
- HEMANGIOSARCOMA	2.0				
- STROMAL SARCOMA	2.0				
OVARIES	50	50	50	50	50
- TUBULAR ADENOMA	6.0				
- LUTEOMA	2.0				
- THECA/GRANUL.C.TUMOR				2.0	
- TERATOMA	2.0				
VAGINA	50	50	50	50	48
- SEBACEOUS ADENOMA		2.0			
KIDNEYS	50	50	50	50	50
- CARCINOMA	2.0				
- HEMANGIOSARCOMA		2.0			
URINARY BLADDER	50	49	49	49	50
- HEMANGIOMA				2.0	
ADRENAL GLANDS	50	49	50	49	50
- PHEOCHROMOCYTOMA	2.0	2.0			2.0
- CORTICAL ADENOMA			2.0		
PANCREAS	50	49	50	50	50
- ISLET CELL ADENOMA					4.0

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TEST ARTICLE : B8610-023 PATHOL. NO.: 92003
TEST SYSTEM : MOUSE, CARCINOGENICITY STUDY, DATE : 25-NOV-92
SPONSOR : BYK GULDEN, HAMBURG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX IN %
STATUS AT NECROPSY: KO, INCL. +

SEX :					FEMALE
DOSE GROUP:	K1	K2	N	M	H
NO.ANIMALS:	50	50	50	50	50
SPLEEN	50	50	50	50	50
- HEMANGIOSARCOMA					4.0
- METASTATIC SARCOMA		2.0			
- HEMANGIOMA		2.0		2.0	
LIVER	50	50	50	50	50
- CARCINOMA, HEPATOC.	6.0		2.0	2.0	16.0
- ADENOMA, HEPATOC.	4.0	10.0	8.0	4.0	14.0
- HEMANGIOSARCOMA		2.0	2.0		
- METASTATIC SARCOMA		2.0			
HEMOLYMPHORET. SYS.	50	50	50	50	50
- MALIGNANT LYMPHOMA	40.0	38.0	36.0	42.0	26.0
SKIN	49	50	48	50	49
- HEMANGIOSARCOMA		2.0			2.0
- SEBACEOUS ADENOMA	2.0				
- BASAL CELL CARCINOMA			2.1		
- SQUAMOUS C.CARCINOMA			2.1		
- KERATOACANTHOMA		2.0			
- HEMANGIOMA				2.0	
MAMMARY GLAND AREA	49	50	48	50	49
- ADENOCARCINOMA		2.0	2.1	8.0	2.0
- ADENOMA		2.0			2.0
- HEMANGIOSARCOMA					2.0
THYROID GLAND	50	50	50	50	50
- FOLLICULAR ADENOMA	2.0	4.0		6.0	
TONGUE	50	50	50	50	50
- PAPILLOMA					2.0
HARDERIAN GLANDS	50	50	50	50	50
- ADENOMA	2.0	10.0	8.0	4.0	

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TEST ARTICLE : B8610-023 PATHOL. NO.: 92003
TEST SYSTEM : MOUSE, CARCINOGENICITY STUDY, DATE : 25-NOV-92
SPONSOR : BYK GULDEN, HAMBURG PATHDATA SYSTEM V3.5d

NUMBER OF ANIMALS WITH NEOPLASTIC LESIONS BY ORGAN/GROUP/SEX IN %
STATUS AT NECROPSY: KO, INCL. +

SEX :					FEMALE
DOSE GROUP:	K1	K2	N	M	H
NO.ANIMALS:	50	50	50	50	50
PITUITARY GLAND	49	50	49	50	50
- ADENOMA	6.1	6.0	8.2	10.0	2.0
LUNGS	50	50	50	50	50
- BRONCH./ALV. TUMOR	2.0	8.0	4.0	14.0	2.0
- METASTATIC CARCINOMA	2.0	2.0			
- METASTATIC SARCOMA		2.0			
STOMACH	50	50	50	50	50
- PAPILLOMA		2.0		2.0	
- SQUAMOUS C.CARCINOMA		2.0			
- ADENOMATOUS POLYP	2.0	2.0	2.0		
LARGE INTESTINE	50	50	50	50	50
- LEIOMYOSARCOMA		2.0		2.0	
BONE	50	50	50	50	50
- OSTEOSARCOMA		2.0			
- OSTEOMA		2.0			
- OSTEOCHONDROSARCOMA					2.0
LYMPH NODES	10	6	9	16	10
- HEMANGIOMA					10.0
BONE MARROW	50	50	49	50	50
- METASTATIC SARCOMA		2.0			

APPEARS THIS WAY
ON ORIGINAL