2 PAGE(S) REDACTED

4. "Based upon results presented in Table 1, the sponsor concluded that ^{32}P-postlabeling studies with pantoprazole were negative, and hepatocarcinogenesis observed in the carcinogenicity study with Sprague Dawley rats could be attributed to a nongenotoxic mechanism."

Evaluation: The sponsor has conducted genotoxicity, chronic toxicology, carcinogenicity, and toxicodynamic studies that suggest these liver tumors could be due to a genotoxic mechanism(s).

Pantoprazole produced positive genotoxic responses with the CHO/HGPRT assay, human lymphocyte chromosomal aberration assay, and in vivo covalent DNA binding assay. ———— in preliminary studies (see Figure 4 above) appear to clearly suggest the presence of a distinct DNA adduct spot with pantoprazole samples prepared from livers of rats that received 200 mg/kg/day for 4 weeks. Thus, pantoprazole could be considered potentially positive in the ^{32}P-Postlabeling assay. Positive responses with the ^{32}P-Postlabeling assay and in vivo covalent DNA binding assay raise the concern that pantoprazole may covalently interact with DNA.

Treatment of Sprague Dawley rats with pantoprazole produced hepatocellular adenomas and carcinomas in the 6- and 12-month oral toxicology studies as well as the 24-month carcinogenicity study. In the 6-month oral toxicity study with Sprague Dawley rats, a hepatocellular adenoma was observed with the high dose at 320 mg/kg/day. In the 12-month oral toxicity study with Sprague Dawley rats, treatment with the low dose at 5 mg/kg/day produced a hepatocellular adenoma and a hepatocellular carcinoma in separate animals.

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 with Sprague Dawley rats, only pantoprazole produced hepatocellular adenomas and carcinomas, 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 (i.e., a nongenotoxic mechanism of hepatocarcinogenesis). Further, it should be noted that the in vivo DNA covalent binding and ^{32}P-Postlabeling assays both suggested that pantoprazole directly interacted with hepatic DNA in a covalent manner.

SUMMARY AND EVALUATION

Pantoprazole is an inhibitor of gastric parietal cell H^+,K^+-ATPase under development for treatment of gastroesophageal reflux disease (GERD). In the present submission, the sponsor has responded to a request from the Division dated April 13, 1999 regarding ^{32}P-Postlabeling Studies presented in General Technical Report (GTR) #32977 (in Volume 1.077 of NDA 20,987). The amendment contains supporting material regarding detailed methodology, _____ for each samples, and quantitation of individual DNA adduct spots within each _____

In GTR-32977, the sponsor assessed the nature of hyperplastic and hypertrophic changes in the liver and the potential for DNA damage in female Sprague Dawley rats following treatment with pantoprazole, omeprazole, or lansoprazole. The potential for DNA damage was assessed using the ^{32}P-postlabeling technique. Rats received the vehicle, pantoprazole at 200 mg/kg/day, omeprazole at 200 or 600 mg/kg/day, or lansoprazole at 200 or 1200 mg/kg/day by the oral route for 4 weeks.

The sponsor has stated that systemic exposure for omeprazole at 600 mg/kg/day and lansoprazole at 1200 mg/kg/day were similar to pantoprazole at 200 mg/kg/day. In a 6-month dose range finding study with pantoprazole in Sprague-Dawley rats, 200 mg/kg/day was identified as the maximum tolerated dose. Doses of omeprazole (200 and 600 mg/kg/day) and lansoprazole (200 and 1200 mg/kg/day) selected for this study were unusually high and exceeded the highest doses used with respective carcinogenicity studies in Sprague Dawley rats (i.e., > maximum tolerated dose). Based upon toxicity endpoints, pantoprazole at 200 mg/kg/day cannot be equated to omeprazole at 600 mg/kg/day or lansoprazole at 1200 mg/kg/day. In a 6-month dose range finding study, omeprazole at 138 mg/kg/day produced significant histopathological changes in the bone marrow, lungs, and liver. In a 3-month dose range finding study, lansoprazole at 300 or 600 mg/kg/day produced severe impairments of body weight gain and significant histopathological changes in the testes, bone marrow, spleen, thymus, and kidney. Systemic exposure to the parent compound for pantoprazole at 200 mg/kg/day and omeprazole at 600 mg/kg/day were roughly equivalent on μg*hr/mL basis; however, plasma levels of the parent compound for lansoprazole at 1200 mg/kg/day were not determined. It must be emphasized that systemic exposure is defined by the summation of AUCs for the parent compound plus its metabolites. The sponsor has not determined metabolite levels for any of these three compounds.

Potential DNA damage in the liver produced by treatment with pantoprazole, omeprazole, or lansoprazole was assessed using the ^{32}P-Postlabeling technique. _____ obtained in preliminary experiments suggested the presence of a distinct DNA adduct spot with pantoprazole samples prepared from livers of rats treated with pantoprazole at 200 mg/kg/day for 4 weeks. Samples in these preliminary studies were prepared using a nuclease P1 enhancement procedure followed by separation in solvent system 1 (i.e., a solvent system used for separation of products with characteristics similar to _____-DNA adducts). The sponsor subsequently

reassessed samples by using solvent system 1, but without the prior use of a DNA adduct enhancement procedure. This data suggested no quantitative differences between the pantoprazole adduct spot and an equivalent corresponding control area. The lack of use of the nuclease P1 enhancement procedure in these studies designed to quantify DNA adducts may have obscured results and dampened a potential positive response for pantoprazole. Enzymatic labeling efficiency of nucleotide-adducts can vary significantly from that observed with normal nucleotides (Mutagenesis 8: 121-126, 1993; Carcinogenesis 18:2367-2371, 1997; Chemical Research in Toxicology 12: 68-77, 1999; and Chemical Research in Toxicology 12: 93-99, 1999). An adduct enrichment procedure, such as the nuclease P1 enhancement procedure, may be essential to labeling adducts due to difference in labeling efficiency. Potentially, all ^{32}P-ATP available in the reaction could be consumed by labeling normal nucleotides before any nucleotide-adducts are labeled in the absence of an adduct enrichment procedure.

The sponsor provided photocopies and hand-drawn diagrams of [redacted] used for quantifying DNA adducts. In general, these [redacted] were impossible to interpret. Referring to hand-drawn diagrams, resolution of adducts appeared to be poor and it is difficult to understand how the sponsor was able to subdivide large spots (i.e., masses) into individual adduct spots. This data as presented was impossible to interpret and added little assistance in interpretation of experiments.

The sponsor considered ^{32}P-postlabeling studies with pantoprazole to be negative due to lack of quantifiable differences with corresponding controls and proposed that hepatocarcinogenesis observed in the carcinogenicity study with Sprague Dawley rats could be attributed to a nongenotoxic mechanism. However, the sponsor has conducted genotoxicity, chronic toxicology, carcinogenicity, and toxicodynamic studies that suggest these observed liver tumors were due to a genotoxic mechanism(s). Pantoprazole produced positive genotoxic responses with the CHO/HGPRT assay, human lymphocyte chromosomal aberration assay, and in vivo covalent DNA binding assay. Treatment of Sprague Dawley rats with pantoprazole has produced hepatocellular adenomas and carcinomas in the 6- and 12- month toxicology studies as well as the 24-month carcinogenicity study. In the 6-month oral toxicity study with Sprague Dawley rats, a hepatocellular adenoma was observed with the high dose at 320 mg/kg/day. In the 12-month oral toxicity study with Sprague Dawley rats, treatment with the low dose at 5 mg/kg/day produced a hepatocellular adenoma and a hepatocellular carcinoma in separate animals. 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.

APPEARS THIS WAY
ON ORIGINAL

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 with Sprague Dawley rats, only pantoprazole produced hepatocellular adenomas and carcinomas, 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 (i.e., a nongenotoxic mechanism of hepatocarcinogenesis). It should be noted that the in vivo DNA covalent binding and ^{32}P-Postlabeling assays both suggested that pantoprazole directly interacted with hepatic DNA in a covalent manner.

RECOMMENDATIONS: The following information should be communicated to the sponsor for their consideration and response.

1. With reference to GTR-32977, _____ displayed in Figure 4 (Volume 1.077, Page 35) suggest the presence of DNA adducts in liver DNA obtained from rats treated with pantoprazole at 200 mg/kg/day. For Figure 4, it appears that all samples were analyzed using the nuclease P1 enhancement procedure prior to enzymatic ^{32}P-labeling and separation in solvent system 1. For subsequent quantitation of DNA adducts as presented in Table 1 (Volume 1.077, Page 36), samples were assessed using solvent system 1, but without the nuclease P1 enhancement procedure prior to enzymatic ^{32}P-labeling. Enzymatic labeling efficiency of nucleotide-adducts can vary significantly from that observed with normal nucleotides (Mutagenesis 8: 121-126, 1993; Carcinogenesis 18:2367-2371, 1997; Chemical Research in Toxicology 12: 68-77, 1999; and Chemical Research in Toxicology 12: 93-99, 1999). An adduct enrichment procedure, such as the nuclease P1 enhancement procedure, may be essential to labeling adducts due to difference in labeling efficiency. Potentially, all ^{32}P-ATP available in the reaction could be consumed by labeling normal nucleotides before any nucleotide-adducts are labeled in the absence of an adduct enrichment procedure. The sponsor should consider quantifying DNA adducts with and without an adduct enrichment procedure (i.e., nuclease P1 enhancement procedure and/or butanol extraction).

2. For the purposes of quantitation, the sponsor has expressed all results as adducts per 10^8 nucleotides. Are the sponsor sure that the units are not actually relative adduct labeling (RAL)?

3. Spot 1 in Figure 4 (Volume 1.077, Page 35) is reported as a background indigenous spot; however, it might be an artifact due to the fact that it is not observed in Figure 4 panel E. Were controls conducted in the absence of DNA and/or DNA from another source (i.e., calf thymus, salmon sperm)? These experiments need to be done before claims can be made about background spots.

4. What were the plate exposure times for data presented in Figure 4 (Volume 1.077, Page 35) and Table 1 (Volume 1.077, Page 36)?

/S/ 5-21-99
Timothy W. Robison, Ph.D. Date

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

/S/
5/30/99

R/D Init.: J. Choudary 5/14/99

TWR/hw/5/21/99

APPEARS THIS WAY
ON ORIGINAL

CSO/Walsh

NDA 20,987

ADDENDUM TO PHARMACOLOGY REVIEW (DATED April 20, 1999) OF NDA 20,987

APR 27 1999

Corrections and/or Additional Information are Included for the Following Studies:

1. Additional information regarding the Incidence of Granulocytic Leukemia in the Fischer Rat Carcinogenicity Study and Statistical Reanalysis of this Study by the Sponsor in Accordance to the Request of the Division to Use the Biometrics Program, Pages 194-204 of Original Review.

2. Correction and additional information for the study entitled "90-Day Dose Range Finding Study with the Thiol Metabolite (B8401-026) in Rats: Comparison with Pantoprazole" (GTR-33264), Pages 114-122 of Original Review.

3. Correction to study entitled "Study for Assessing the Tumor Promoting Activity of Pantoprazole in Stomach and Forestomach in Sprague Dawley Rats" (GTR-33036), Pages 210-218 of Original Review.

4. Additional information for the study entitled "Studies on the Hepatic Effects of Pantoprazole, Lansoprazole, and Omeprazole in Rats Including ^{32}P-Postlabeling Experiments" (GTR-32977), Pages 248-255 of Original Review.

TOXICOLOGY:

Incidence of Granulocytic Leukemia in the Fischer Rat Carcinogenicity Study and Statistical Reanalysis of this Study by the Sponsor in Accordance to the Request of the Division to Use the Biometrics Program, Pages 194-204 of Original Review.

In a 2-year carcinogenicity study, Fischer F-344 rats received pantoprazole by the oral route of administration at doses of 5, 15, and 50 mg/kg/day (GTR-31898 and GTR-31545). There were two control groups, an untreated control group and a vehicle-treated control group. For the hematopoietic system, the sponsor separately reported the incidences of granulocytic leukemia, histiocytic sarcoma, LGL leukemia, and unclassified lymphoma/leukemia. LGL leukemia is a common neoplastic lesion for Fischer rats. The incidences of histiocytic sarcoma, LGL leukemia, and unclassified lymphoma/leukemia displayed no relationship to treatment. Granulocytic leukemia, a rare tumor in Fischer rats as suggested by the recent reference entitled F344/N Rats: Tumor Incidence in Control Animals by Route and Vehicle of Administration prepared for the National Institute of Environmental Health Science (February 1998), displayed an incidence that appeared to have a relationship to treatment and does not appear to be a background event as stated on page 202 of the original review. Incidence of neuroendocrine tumors (benign and malignant) and granulocytic leukemia in male and female treatment groups and their levels of statistical significance are shown in the tables below. Statistical analysis was performed by the sponsor. A FDA statistician's analysis was unavailable at the time of this review.

Neoplastic lesions in male Fischer F-344 rats that received pantoprazole by the oral route at doses of 5, 15, and 50 mg/kg/day. There were two control groups, an untreated control group and a vehicle-treated control group (UC = Untreated Control; VC = Vehicle-treated Control; and HC = Historical Control).

Organ/Tumor	UC	VC	5	15	50	p-value[B]	HC[C]
Glandular stomach (fundus) -neuroendocrine tumor (B)	0/50	0/49	0/50	2/50	5/50	0.001	-
pairwise comparison vs VC[A]	*p=0.500*		*p=0.500*	*p=0.099*	*p=0.009*		
Glandular stomach (fundus) -neuroendocrine tumor (M)	0/50	0/49	0/50	2/50	2/50	0.049	-
pairwise comparison vs VC	*p=0.500*		*p=0.500*	*p=0.089*	*p=0.064*		
Glandular stomach (fundus) -neuroendocrine tumor (B + M)	0/50	0/49	0/50	4/50	7/50	0.001	-
pairwise comparison vs VC	*p=0.500*		*p=0.500*	*p=0.030*	*p=0.002*		
Granulocytic leukemia -original reported incidence -incidence used for statistical analysis	0/27 0/50	0/16 0/50	0/21 0/50	1/20(5%) 1/50(2%)	2/27(7.4%) 2/50(4%)	- 0.030	0/50 0/402
pairwise comparison vs VC	*p=0.500*		*p=0.500*	*p=0.186*	*p=0.085*		

A. Pairwise one sided Peto comparisons to Vehicle Control (It was unclear if Fisher's exact test was used).
B. One-sided Peto test for trend using dose proportional scores (0, 5, 15, 50) versus vehicle-treated control.
C. First value is water gavage-historical control (n = 50). Second value is corn oil gavage historical control. These historical control values are quoted from the F344/N Rats: Tumor Incidence in Control Animals by Route and Vehicle of Administration prepared for the National Institute of Environmental Health Science (February 1998).

Neoplastic lesions in female Fischer F-344 rats that received pantoprazole by the oral route at doses of 5, 15, and 50 mg/kg/day. There were two control groups, an untreated control group and a vehicle-treated control group (UC = Untreated Control; VC = Vehicle-treated Control; and HC = Historical Control).

Organ/Tumor	UC	VC	5	15	50	p value[B]	HC
Glandular stomach (fundus) -neuroendocrine tumor (B)	0/49	0/50	2/50	9/50	4/50	0.078	-
pairwise comparison vs VC	*p=0.500*		*p=0.050*	*p=0.001*	*p=0.007*		
Glandular stomach (fundus) -neuroendocrine tumor (M)	0/49	0/50	2/50	3/50	3/50	0.106	-
pairwise comparison vs VC	*p=0.500*		*p=0.050*	*p=0.043*	*p=0.043*		
Glandular stomach (fundus) -neuroendocrine tumor (B + M)	0/49	0/50	4/50	12/50	7/50	0.022	-
pairwise comparison vs VC	*p=0.500*		*p=0.008*	*p<0.001*	*p=0.001*		

A. Pairwise one sided Peto comparisons to vehicle control (It was unclear if Fisher's exact test was used).
B. One-sided Peto test for trend using dose proportional scores (0, 5, 15, 50) versus vehicle-treated control.

Evaluation: Benign and malignant neuroendocrine tumors observed in male rats at doses of 15 and 50 mg/kg/day and female rats at doses of 5, 15, and 50 mg/kg/day display a clear relationship to treatment. Granulocytic leukemia, a rare tumor, was found in 1 male at 15 mg/kg/day and 2 males at 50 mg/kg/day. The number of animals examined for granulocytic leukemia in each group was not clear. Numbers examined per group in volume 1.062, page 23 of the NDA submission do not match those used in the statistical analysis. The original number of male rats that were reported to have been examined in volume 1.062, page 23 are listed first in the table. The second line lists the incidence used for statistical analysis. The sponsor has not reported a reanalysis of groups for granulocytic leukemia. The incidence of granulocytic leukemia in the male 15 and 50 mg/kg/day groups exceeded historical control background levels. Using a n of 50 per group, pairwise one sided Peto comparison of incidences in the 15 and 50 mg/kg/day groups to the vehicle control were not statistically significant as might be expected for a rare tumor; however, the trend test comparison to the vehicle control suggests a possible relationship to treatment. Further, reanalysis at appropriate incidence rates may yield a relationship to treatment.

90-Day Dose Range Finding Study with the Thiol Metabolite (B8401-026) in Rats: Comparison with Pantoprazole (GTR-33264), Pages 114-122 of Original Review.

The following item requires correction.

Under Blood Biochemistry on Page 117 of the original review, a depression of TSH levels was reported for male and female rats that received pantoprazole at 200 mg/kg/day. The wrong control group (i.e., propylene glycol in a 3% suspension of methocel E15 in distilled water) was used in calculation of the percent of control for female rats. The control group receiving distilled water, pH 10.7-10.9 should have been used. The text should be corrected as follows below. The second and third sentences provides additional information regarding the interpretation of this data.

TSH levels at weeks 11/12 for male and female rats that received pantoprazole at 200 mg/kg/day were decreased to 29.6 and 7.7% of the control (1.89 ± 3.35 and 5.61 ± 7.67 mU/L), respectively; however, there was significant variation within groups and these changes were not statistically significant. The depression of TSH levels is the opposite of that predicted, based upon the observed induction of UDP-glucuronyl transferase activity and potentially enhanced metabolism of thyroxine (T_4). Increased metabolism of T_4 might be expected to result in a compensatory increase in TSH levels.

Study for Assessing the Tumor Promoting Activity of Pantoprazole In Stomach and Forestomach in Sprague Dawley Rats (GTR-33036), Pages 210-218 of Original Review.

The following items requires correction.

Under Histopathology for Neoplastic Lesions on Page 215 of the Original Review, the incidence of hepatocellular adenoma and carcinoma were incorrectly reported. In the table reporting tumor incidence on Page 216 of the original review, a C-cell adenoma that occurred in one female in the NMU + vehicle of phenobarbital group was inadvertently left out. It should be noted that the incidences of hepatocellular adenoma + carcinoma and thyroid gland C-cell adenoma displayed no relationship to treatment and had no impact on the interpretation of the study. The text and table should be corrected as follows below.

Neoplastic Lesions: For the liver, hepatocellular adenoma and carcinoma were observed in female treatment groups and the combined incidence was as follows: 8.3% (2/24) for female rats that received NMU + pantoprazole; 4.2% (1/24) for female rats that received NMU + phenobarbital; and 4.2% (1/24) for female rats that received NMU + vehicle of pantoprazole.

Tumor incidence by organ for control rats and rats that received NMU + pantoprazole, NMU + vehicle of pantoprazole, vehicle of NMU + pantoprazole, NMU + phenobarbital, NMU + vehicle of phenobarbital, and vehicle of NMU + phenobarbital (n = 24 per group).

Tissue	Control		NMU + Pantoprazole		NMU + Vehicle of Pantoprazole		Vehicle of NMU + Pantoprazole		NMU + Phenobarbital		NMU + Vehicle of Phenobarbital		Vehicle of NMU + Phenobarbital	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Liver														
-hepatocellular carcinoma (M)	0	0	0	0	0	0	0	0	0	1	0	0	0	0
-hepatocellular adenoma (B)	0	0	0	2	0	0	0	0	0	0	0	1	0	0
-cholangioma(B)	0	0	0	0	0	0	0	1	0	0	0	0	0	0
Thyroid gland														
-C-cell adenoma (B)	0	1	1	1	1	1	1	1	2	0	0	1	0	0
-follicular cell adenoma	0	0	2	0	0	0	0	0	1	0	0	0	1	0

APPEARS THIS WAY
ON ORIGINAL

SUMMARY AND EVALUATION

In a two year carcinogenicity study, Fischer F-344 rats received pantoprazole by the oral route of administration at doses of 5, 15, and 50 mg/kg/day. Benign and malignant neuroendocrine tumors were observed in the gastric fundus of male rats at doses of 15 and 50 mg/kg/day and female rats at doses of 5, 15, and 50 mg/kg/day. Statistical reanalysis clearly related incidences of benign and malignant neuroendocrine tumors to pantoprazole treatment. Granulocytic leukemia, a rare tumor in Fischer 344 rats, occurred in male rats at doses of 15 and 50 mg/kg/day. The incidences of granuolcytic leukemia reported for male treatment groups in volume 1.062, page 23 of the NDA submission does not match those used by the sponsor in the statistical analysis. The sponsor has not reported a reanalysis of groups for granulocytic leukemia after the original report. With a n of 50 per group, the incidence of granulocytic leukemia for male at 15 and 50 mg/kg/day was not statistically significant as might be expected for a rare tumor; however, a significant trend test versus the vehicle control as well as its occurrence in the mid and high dose groups at levels exceeding historical background rates may suggest a relationship to treatment. Further, an analysis of this data by a FDA statistician at correct incidence rates may yield a different result.

RECOMMENDATION: The sponsor should be requested to provide information regarding the carcinogenicity study with pantoprazole in Fischer 344 rats as listed below.

1. The sponsor should clarify the number of animals per group in the Fischer rat carcinogenicity study that were examined for granulocytic leukemia. If a reanalysis of the incidence of granulocytic leukemia was performed in treatment groups after the original report, the sponsor should provide information regarding the testing facility, study dates, GLP compliance, and procedures used.

2. The sponsor should be asked to provide the spontaneous tumor incidences for Fischer 344 rats in the testing facility over the period of 1990 to 1995.

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

4-27-99
Date

cc:
Orig NDA 20,987
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Robison
HFD-180/Dr. Gallo-Torres
HFD-715/Dr. Lin
HFD-715/Dr. Guo

TWR/hw/4/27/99

/S/ 4/27/99

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ON ORIGINAL

NDA 20,987

C80/1Vol1

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

REVIEW # 1

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

APR 20 1999

Date of Submission: Original: June 30, 1998
Amendment: December 18, 1998
Amendment: January 28, 1999

Date of HFD-180 Receipt: Original: July 2, 1998
Amendment: December 21, 1998
Amendment: January 29, 1999

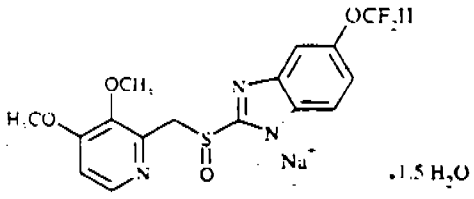
Date of Review: April 13, 1999

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA

ORIGINAL SUMMARY

Drug: PROTONIX™ (Pantoprazole Sodium, B8610-23, — 96022) Enteric-Coated Tablets, 40 mg

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



Molecular Formula: $C_{16}H_{14}F_2N_3NaO_4S \times 1.5\ H_2O$
Molecular Weight: 432.4

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Formulation:

Each tablet contains the following ingredients.

Active Ingredient	Claim/Dosage Unit	Input/Dosage Unit
Pantoprazole sodium sesquihydrate	40 mg anhydrous	45.1 mg[1]
Inactive Ingredients of Core		
Mannitol, USP		
Crospovidone, NF		
Povidone USP		
Sodium Carbonate Anhydrous, NF		
Calcium Stearate, NF		
Hydroxypropyl Methylcellulose USP		
Povidone USP		
Titanium Dioxide, USP		
Yellow Ferric Oxide, NF		
Propylene Glycol, USP		
Eudragit L30D-55[3]		
Triethyl Citrate, NF		

Notes

1. 45.1 mg sodium salt sesquihydrate is equivalent to 40 mg anhydrous pantoprazole
2.
3. Eudragit L30D-55 comprises the following:
   - Methacrylic Acid Copolymer, NF
   - Sodium Lauryl Sulfate, NF
   - Polysorbate 80, NF

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

Related Drugs/INDs/NDAs/MFs: IND and Byk Gulden GmbH of Konstanz, Germany; IND from Wyeth-Ayerst Research of Philadelphia, PA; and NDA 20,988 from Wyeth-Ayerst Research of Philadelphia, PA.

Proposed Marketing Indication: PROTONIX enteric-coated tablets are indicated for the short-term treatment (4 to 8 weeks) of gastroesophageal reflux disease. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of PROTONIX may be considered.

Dose: The recommended adult oral dose is 40 mg given once daily.

Preclinical Studies and Testing Laboratories:

STUDY	GTR #	TESTING LABORATORY	DRUG BATCH	PAGE #
PHARMACOLOGY[A,R,S]:				12-29
ABSORPTION, DISTRIBUTION, METABOLISM, AND EXCRETION:				
ABSORPTION				
Mouse				
Pharmacokinetics of radiolabeled pantoprazole, omeprazole, and lansoprazole in mice after a single intragastric dose[R].	27726			30-31
Pharmacokinetics of pantoprazole after a single intragastric dose[A].	27900			31
Pharmacokinetics of radiolabeled pantoprazole, omeprazole, and lansoprazole in mice after multiple intragastric dose[A].	27865			31-32
Rat				
Pharmacokinetic studies in male rats after a single dose[A].	31547			32-33
Pharmacokinetics of pantoprazole following single and multiple oral administration[A,R].	31322			33
[redacted] detection of the thiol metabolite in rat plasma and serum[R].	31324			34
Absorption and bioavailability of pantoprazole, omeprazole, and lansoprazole following 1 or 7 oral doses[R].	31305			34-36
Stereoselective chiral inversion of pantoprazole enantiomers[R].	32139			36-38
Dog				
Kinetics and bioavailability after single oral doses of solution and uncoated and enteric-coated tablets[R].	31190			38-39
Pharmacokinetics of pantoprazole and its sulfone metabolite in the dog following single and repeated oral and intravenous doses[R].	31546			39-40
Monkey				
Absorption of ^{14}C-pantoprazole following oral and intravenous administration[R].	31549			40-42
DISTRIBUTION				
^{14}C-pantoprazole binding to rat, dog, and human serum proteins[R,S].	31194			42
In vitro binding of pantoprazole, omeprazole, and lansoprazole in human, rat, and mouse plasma[R,S].	27796			43
Estimation of plasma:whole blood concentration ratios in vitro using rat, dog, and human blood[R].	31199			43

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Rat				
Quantitative distribution of ^{14}C-pantoprazole (^{14}C at 2-position of benzimidazole ring) after a single oral administration[R].	31197			44
Whole body ——— study after a single oral or intravenous administration of [^{14}C-Pyridyl]-pantoprazole[A].	31326			44-45
Melanin binding of radioactivity in male pigmented rats following intravenous or oral administration of ^{14}C-pantoprazole at 5 mg/kg (^{14}C at 2-position of benzimidazole ring)[R].	31198			45
Whole body ——— study on the distribution of radioactivity following intravenous or oral administration of ^{14}C-pantoprazole (^{14}C at 2-position of benzimidazole ring)[R].	31223			45-46
Transplacental transport and mammoglandular passage of ^{14}C-pantoprazole (^{14}C at 2-position of benzimidazole ring)[A].	31203			46-47
Quantitative distribution of radioactivity after a single intravenous administration of ^{14}C-pantoprazole (^{14}C at 2-position of benzimidazole ring)[R].	31224			47-48
Distribution of [^{14}C-Pyridyl]-pantoprazole in organs and tissues of male rats after a single intravenous administration[A].	31314			48-50
Monkey				
Distribution of ^{14}C-pantoprazole[R].	31549			51-52
METABOLISM				
Enzyme Inhibition and Induction-In Vitro				
Inhibition of hydroxylation of lonzolac (Cytochrome P450 Dependent Reaction)[A].	31210			52-53
Interaction with ethylmorphine demethylase activity (Cytochrome P450) in rat liver microsomes[R].	31211			53
Influence on 7-ethoxycourmarin dealkylase activity (Cytochrome P450) in rat liver microsomes[R].	33324			53
Effect of 7-ethoxycoumarin dealkylase activity-Cytochrome P450 in rat liver microsomes[A].	31209			53
Interaction with lonazolac in human microsomes[R].	31217			53-54
Interaction of omeprazole, pantoprazole, and another proton pump inhibitor with rat liver cytochrome P450 in vitro[R].	31206.			54
An evaluation of the CYP1A induction potential using primary rat hepatocytes and comparison with other proton pump inhibitors[R].	31189			54-55
An evaluation of the Cytochrome P450 induction potential using primary rat hepatocytes and comparison with other proton pump inhibitors[R].	32138			55-56
Identification of Cytochrome P450 isozymes involved in the metabolism of pantoprazole with human liver microsomes[A].	23/96 K1			56
Biotransformation of pantoprazole in human microsomes. Identification of P450 isozymes by selective inhibitors[A].	31216			56-57

APPEARS THIS WAY ON ORIGINAL

Enzyme Inhibition and Induction-In Vivo				
Interactions of cimetidine, omeprazole, lansoprazole, or pantoprazole with diazepam in rats[A].	31212			57
Induction of ethylmorphine demethylase activity after oral administration to female rats for 3 days[R].	31215			57
Effects on the drug-metabolizing enzyme system in rat liver[A].	31544			58-60
Effects of pantoprazole and the thiol metabolite on selected hepatic drug metabolizing enzyme activities following oral administration to female rats for 4 weeks[A].	31321			60-61
Effects on selected hepatic drug-metabolizing enzyme activities after oral administration to female rats for 4-weeks followed by a 4-week recovery.	31304			62
Rats and Dogs-Metabolism Characteristics and Metabolites				
Biotransformation of ^{14}C-pantoprazole in selected organs of the rat[R].	31302			62-63
Metabolic fate of ^{14}C-pantoprazole in rats after an oral dose of 5 or 500 mg/kg[A,R].	31317			63-67
Metabolism of ^{14}C-pantoprazole in rats following a single oral or intravenous administration[A,R].	31202			67-70
Metabolism of ^{14}C-pantoprazole in rats following a single oral or intravenous administration[A].	31325			70-71
Metabolism of ^{14}C-pantoprazole in rat and dog[R].	31201			71-72
Metabolic fate of ^{14}C-pantoprazole in dogs after an oral dose[A,R].	31316			73-74
EXCRETION				
Mouse				
Excretion of radioactivity in mice after oral administration of ^{14}C-pantoprazole[A].	31315			74
Rat				
Kinetics in blood and balance excretion in rats after oral dosing with ^{14}C-pantoprazole[R].	31196			75
Kinetics in blood and balance excretion after multiple oral administration of ^{14}C-pantoprazole[R].	31196			76
Balance, excretion, and pharmacokinetic study in male rats following oral and intravenous administration of [^{14}C-Pyridyl]-pantoprazole[A].	31310			77
Kinetics in blood and balance excretion in rats after intravenous dosing with ^{14}C-pantoprazole[R].	31218			77-78
Biliary excretion and metabolism of ^{14}C-pantoprazole in rats[A].	31328			78
Dog				
Balance excretion and pharmacokinetic study in male beagle dogs following oral and intravenous administration of ^{14}C-pantoprazole[R].	31191			78-79
Monkey				
Excretion of radioactivity following oral and intravenous administration of ^{14}C-pantoprazole[R].	31549			79-80

APPEARS THIS WAY ON ORIGINAL

TOXICOLOGY:				
ACUTE TOXICITY IN MICE, RATS, AND DOGS				
Acute toxicity of pantoprazole in mice, rats, and dogs following oral or intravenous administration[A,R,S].	31633 31634 31635 31636 31637 31638 31639 31640 32136 31650 31642 31643	Byk Gulden Konstanz, Germany [redacted]	489065 489065 K23/144 K23/144 K23/144 K23/144 589085 589085 294160 513150 033927 349235 589085 589085	83-86
Acute intravenous toxicity of (+)Enantiomer in mice[A].	31644	Byk Gulden Konstanz, Germany		86
Acute intravenous toxicity of (-)Enantiomer in mice[A].	31645	Byk Gulden Konstanz, Germany		86-87
Acute oral toxicity of the thiol metabolite in rats[A].	32262			87
Acute intravenous toxicity of [redacted] in mice and rats[R].	31648 31649	Byk Gulden Konstanz, Germany	K33/141-1	87-88
RAT				
Subacute Toxicology				
Intravenous Route of Administration				
4-Week intravenous toxicity study[A].	31901	Byk Gulden Konstanz, Germany	K19/271-3	89-91
4-Week intravenous toxicity study-local tolerance[A].	32004	Byk Gulden Konstanz, Germany	K21-120A	91
4-Week intravenous toxicity study with unstressed batch[R].	32911	Byk Gulden Konstanz, Germany	293610	92-95
4-Week intravenous toxicity study with stressed batch[R].	32910	Byk Gulden Konstanz, Germany	195220	96-100
4-Week intravenous toxicity study with [redacted]	32006	Byk Gulden Konstanz, Germany	Zi20/107A	100-103
Oral Route of Administration				
4-Week oral toxicity study with pantoprazole[S].	31902	Byk Gulden Konstanz, Germany	K23/144	104-107
4-Week oral toxicity study with pantoprazole-serum gastrin levels[A].	31278	Byk Gulden Konstanz, Germany	189025	107-108
4-Week oral toxicity study with thiol metabolite[A].	32263	Byk Gulden Konstanz, Germany	200085	109-111
3-Month oral toxicity study with aged rats (52-57 weeks old)[S].	31984	Byk Gulden Konstanz, Germany	189025	112-114
90-Day oral dose range finding study with thiol metabolite[R].	33264	[redacted]	200085	114-122
Electron microscopic evaluation of female rat liver after 3 month treatment with pantoprazole or thiol metabolite[A].	31821	Byk Gulden Konstanz, Germany	NA	123

Chronic Toxicology				
Oral Route of Administration				
6-Month Oral Toxicity Study[A,S,R].	31379 31372 31320	Byk Gulden Konstanz, Germany	289035	123-129
12-Month oral toxicity study[A,R].	31377 31999 32041	[redacted]	299156	129-134
DOG				
Subacute Toxicology				
Intravenous Route of Administration				
2-Week toxicity study using oral and intravenous routes-special emphasis on toxic effects on the eye and ear[R].	32001	Byk Gulden Konstanz, Germany	BY1023-20-1-1; Ch.B.: 513150	135-138
30-Day intravenous toxicity[A,R].	31904 31193	[redacted]	3 and 4	139-141
4-Week continuous intravenous infusion toxicity study[R].	32002	[redacted] -Byk Gulden Konstanz, Germany	513150	142-149
Oral Route of Administration				
10-Day oral toxicity study[S,R].	32003	[redacted]	3 and 4	149-151
30-Day oral toxicity study[S,R].	32082 31200	[redacted]	5	151-154
Chronic Toxicity				
Oral Route of Administration				
6-Month oral toxicity study[A,R].	31376 31276 31319	Byk Gulden Konstanz, Germany	Dre 1418, 1413, 1415, 1419, and 1446	154-158
1-Year oral toxicity study[A].	32000	[redacted]	399175	158-162
CARCINOGENICITY				
[redacted]				163-165
Design/Protocols for assessing the tumor promoting potential of pantoprazole in liver, thyroid, stomach, and forestomach in rats				166-167
Mouse				
4-Week oral dose range finding study in two strains[A].	31373	Byk Gulden Konstanz, Germany	289035	167-169
4-Week oral dose range finding study[A].	31375	Byk Gulden Konstanz, Germany	289035	169-171
2-Year oral carcinogenicity study in B6C3F1 mice[A].	31899	Byk Gulden Hamburg, Germany	399175	172-179
2-Year oral carcinogenicity study in B6C3F1 mice-toxicokinetic report[R].	31303			180

Rat				
2-Year oral carcinogenicity study in Sprague Dawley rats[A].	31282	[redacted]	299155/89 PD 324, 399-175/89 PD 341/1, and 399-175/89 PD 341/2	181-192
Immunohistological evaluation of neuroendocine tumor metastases from 2-year carcinogenicity study with Sprague Dawley rats[A].	31279			192-193
Number and size and gastric neuroendocrine tumors in 2-year carcinogenicity study with Sprague Dawley rats[A].	31280			193
Two-year oral carcinogenicity study in Fischer 344 rats[A,R].	31898 31545	Byk Gulden Hamburg, Germany	500-205	194-204
Study for assessing the tumor promoting activity of pantoprazole in stomach and forestomach of Sprague Dawley rats[R].	33036	[redacted]	0295220000	204-210
Study for assessing the tumor promoting activity of pantoprazole in liver and thyroid of Sprague Dawley rats[R].	33037	[redacted]	0295220000	210-218
REPRODUCTIVE TOXICOLOGY:				
Rats				
Oral Segment I fertility and reproductive performance study in male rats[S].	32063	[redacted]	58905-88PD477	218-219
Oral Segment I fertility and reproductive performance study in female rats[S].	32062	[redacted]	58905-88PD477	219-221
Intravenous Segment II teratology study in rats[S].	32031	Byk Gulden Hamburg, Germany	K23/161	221-222
Oral Segment II teratology study in rats[S].	32034	Byk Gulden Hamburg, Germany	579-015	223-224
Oral Segment II teratology study in rats[R].	32059	Byk Gulden Hamburg, Germany	500205	224-225
Rabbits				
Intravenous Segment II teratology study in rabbits[S].	32033	Byk Gulden Hamburg, Germany	579-015	226-227
Oral Segment II teratology study in rabbits[S].	32035	Byk Gulden Hamburg, Germany	579-015	227-228
Rats				
Oral Segment III perinatal and postnatal development study in rats[A].	32081	[redacted]	589085-88PD480	229-230
GENOTOXICITY:				
Studies with Pantoprazole.				
Bacterial reverse mutation assay with pantoprazole[S].	32058	[redacted]	4	231
Metaphase chromosomal analysis of human lymphocytes cultured in vitro[S].	32042	[redacted]	4	231-232
Chromosomal aberration assay in human whole blood lymphocytes with pantoprazole[A].	32046 32253	[redacted]	0494180000	232-234
Chromosomal aberration assay in human lymphocytes in vitro with pantoprazole[R].	32044	Byk Gulden Konstanz, Germany	029522000	234-236
Mutagenic potential of pantoprazole in Chinese hamster Ovary/HGPRT Locus Assay[S].	32057	[redacted]	4	236-238
Unscheduled DNA synthesis in primary hepatocytes[A].	32055	[redacted]	109-195	238

AS52/GPT mammalian cell-forward gene mutation assay with pantoprazole[A].	32048	[redacted]	0494180000	239
Cell mutation assay at the thymidine kinase locus in mouse lymphoma L5178Y cells with pantoprazole[A].	32047	[redacted]	0494180000	239-240
Malignant transformation assay with pantoprazole in C3H-M2 mouse fibroblasts in vitro[A].	32053	[redacted]	500205	240-241
In vitro cell transformation assay using Syrian hamster embryo cells[A].	32051	[redacted]	500205	241-242
Mouse micronucleus test with pantoprazole[S].	32056	[redacted]	4	242-243
Mouse micronucleus test with pantoprazole[A].	32054	[redacted]	109195	243-245
Bone marrow chromosomal aberration assay in Sprague Dawley rats with pantoprazole[A].	32049	[redacted]	0494180000	245-246
Potential for DNA binding of pantoprazole[A].	32052	[redacted]	500205	246-247
4-Week oral toxicity study with pantoprazole, omeprazole, and lansoprazole in rats-hepatotoxic effects. Includes a ^{32}P-postlabeling study with hepatic DNA[R].	32977	[redacted] -Byk Gulden Konstanz, Germany		248-255
Studies with the Thiol Metabolite of Pantoprazole (B8401-026).				
Bacterial reverse mutation assay with the thiol metabolite of pantoprazole[A].	32256	Byk Gulden Konstanz, Germany	200085	255-256
Mouse micronucleus test with the thiol metabolite of pantoprazole[A].	32252	Byk Gulden Hamburg, Germany	200085	256-257
Repeat Mouse micronucleus test with the thiol metabolite of pantoprazole[A].	32251	Byk Gulden Hamburg, Germany	292109	257-258
Malignant transformation assay with the thiol metabolite of pantoprazole[R].	32254	[redacted]		258-259
Cell transformation assay using Syrian hamster cells with the thiol metabolite of pantoprazole[R].	32255	[redacted]	292109	259-260
Studies with B [redacted]				
Bacterial reverse mutation assay with [redacted]	32045	[redacted] -Byk Gulden Konstanz, Germany	Zi20/107A	260-261
SPECIAL TOXICITY STUDIES:				
PULMONARY TOXICITY				
Rat				
The effect of pantoprazole, omeprazole, and the thiol metabolite of pantoprazole on the lung after intravenous administration to rats[S].	31983 and 31982	Byk Gulden Konstanz, Germany		262-263
Pulmonary toxicity of the thiol metabolite of pantoprazole in male rats[A].	32260			263

Dog				
Comparison of toxicological response and pharmacokinetic behavior of [redacted] and [redacted] dogs to intravenous and oral treatment with pantoprazole.	32137	[redacted]		263-265
5-Day intravenous toxicity to establish dose/response relationships for effusion of fluid into pulmonary alveoli following intravenous administration of pantoprazole[R].	31987	[redacted] -Byk Gulden Konstanz, Germany	4	266-267
5-Day Intravenous Pulmonary Toxicity Study of pantoprazole and the thiol metabolite of pantoprazole in dogs[S].	31985	[redacted]	589085-88PD477	268-269
EFFECTS ON THYROID GLAND				
Rat				
Effects of pantoprazole on thyroid hormone metabolism and UDPGT induction in rats[A].	31307	[redacted]	500205	269-271
Effects on thyroid function in female rats after 4-week treatment[A].	31720	[redacted]	510235	272
Effects on thyroid function in female rats after 4-week treatment[A].	31306	[redacted]	0295250000 and 122H0143	272-273
Effects on thyroid function in female rats after 4-week treatment-perchlorate discharge test[R].	31719	[redacted]	0295250000	274-277
EFFECTS ON EYES				
Monkey				
28-Day intravenous electroretinographic study	32005 and 31188	[redacted] -Byk Gulden Konstanz, Germany	0296300000	277-280
GASTRIN PROFILE STUDIES				
Rat				
Serum gastrin levels in rats in response to oral treatment with pantoprazole, omeprazole, or lansoprazole[R].	32038	Byk Gulden Konstanz, Germany	0295250000 and 295220000	281-286
Gastrin profile study in Wistar and Sprague Dawley rats after 30-day treatment with pantoprazole[R].	31277	[redacted]	589085	286-287
Comparison of the effects of lansoprazole, pantoprazole and omeprazole on plasma gastrin levels and gastrin-dependent parameters in rat stomach[R].	32030	-Byk Gulden Konstanz, Germany	500205	287-288
SERUM CHOLESTEROL STUDY				
Rat				
Effects of pantoprazole on serum cholesterol in rats after a 60-day treatment period[A,R].	32025	[redacted]	399175	289
MITOGENESIS				
Rat				
Mitogenic action of pantoprazole on rat liver after oral administration for 7 and 14 days[A].	31334	[redacted]	500205	290

ANTIGENICITY/SENSITIZATION STUDIES				
Guinea pig				
Guinea pig maximization test[S].	31995	Byk Gulden Pharmaceuticals		291
Active systemic anaphylaxis and homologous passive cutaneous anaphylaxis tests in guinea pigs[S].	32029	[redacted]	293140	291-292
Guinea pig maximization test with thiol metabolite of pantoprazole[A].	32259	Byk Gulden Pharmaceuticals		292-293
LOCAL TOLERANCE STUDIES				
Rat				
Local toxicity after intramuscular administration[R].	31991 and 31998	Byk Gulden Konstanz, Germany	4F	293
Local toxicity of pantoprazole lyophilisate after intramuscular injection[A].	32024	Byk Gulden Hamburg, Germany	013927	294
Local toxicity of pantoprazole lyophilisate after intramuscular injection[A].	32028	Byk Gulden Hamburg, Germany	425-623	294-295
Rabbit				
Local toxicity after a single intravenous injection[R].	31990 and 31997	Byk Gulden Konstanz, Germany	3 and 4F	295-296
Local toxicity after a single paravenous injection[R].	31988	Byk Gulden Konstanz, Germany	4F	296
Local toxicity after a single intraarterial injection[R].	31989 and 31996	Byk Gulden Konstanz, Germany	3 and 4F	297
Local toxicity of pantoprazole lyophilisate after a single intravenous, paravenous or intra-arterial injection[A].	32027	Byk Gulden Hamburg, Germany	425623	298
Local toxicity of pantoprazole lyophilisate after a single intravenous, paravenous or intra-arterial injection[A].	32039	Byk Gulden Hamburg, Germany	013927	298-299
Acute dermal irritation[A].	32026	Byk Gulden Hamburg, Germany		299
Acute dermal irritation with thiol metabolite[A].	32257	Byk Gulden Hamburg, Germany		300
Acute eye irritation test with thiol metabolite[A].	32258	Byk Gulden Hamburg, Germany		300-301
Dog				
Acute intravenous and perivenous irritancy study[R].	31993	[redacted] -Byk Gulden Hamburg, Germany	Formula 16	301
IN VITRO EFFECTS ON RED BLOOD CELLS				
In vitro human and canine red cell hemolysis study[R].	31994	[redacted] -Byk Gulden Hamburg, Germany	3	302
Effect on membrane stability of human, rat, and dog erythrocytes[R].	31992	Byk Gulden Hamburg, Germany	K23/161	303

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

IND —— dated December 10, 1996 (Document Room Date, May 14, 1997).
R. Study reviewed by Dr. Timothy W. Robison under NDA 20,987.
S. Study reviewed by Dr. Ching-Long Joseph Sun under the Initial Submission of IND —— dated September 13, 1990 (Document Room Date, November 9, 1990).

PHARMACOLOGY:

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. Pharmacology studies with pantoprazole examined in vitro and in vivo inhibition of acid secretion as well as antiulcer activity.

Primary Pharmacology

In Vitro Effects on Gastric Acid Secretion in Isolated Gastric Glands

Inhibition of Acid Secretion (^{14}C-Aminopyrine Accumulation) in Permeable Isolated Rabbit Fundic Glands by Pantoprazole (Na^+ salt: Pantoprazole) (GTR-31465).

Acid secretion induced by KCl and ATP was significantly inhibited by pantoprazole in permeable rabbit fundic glands (IC_{50} = 0.92 μM). Inhibition of acid secretion occurred as a function of time and pantoprazole concentration. Inhibition was irreversible suggesting covalent binding of pantoprazole to the enzyme, H^+,K^+-ATPase.

Inhibition of Cyclic AMP-Stimulated Acid Secretion in Isolated Rabbit Fundic Glands in the Presence of Pantoprazole (GTR-31466, GTR-31467, GTR-31468, GTR-31469).

Acid secretion by rabbit fundic glands in vitro was stimulated by dibutyryl-cyclic AMP, histamine or carbachol. Pantoprazole (free acid or Na-salt) inhibited dibutyryl-cyclic AMP-, histamine-, and carbachol-stimulated acid secretion with IC_{50} values of 2.95 μM. 0.524 μM and 0.28 μM respectively. IC_{50} values of pantoprazole [racemic mixture; 6 μM]. B9010-007 [(+)-enantiomer, 5.98 μM] and B9010-026 [(-)-enantiomer, 6.07 μM] were comparable in the inhibition of histamine-stimulated acid secretion.

Inhibition of H^+-Secretion in K-ATPase Vesicles by Pantoprazole (GTR-31470).

Pantoprazole inhibited ATP-stimulated acid secretion by pig gastric vesicles in the presence of KCl in vitro in a concentration-dependent manner with an IC_{50} value of 4.1 μM.

In Vitro Inhibition of H^+,K^+-ATPase

In Vitro Potency of the (H^+/K^+)-ATPase Inhibitor, Pantoprazole, in Relation to Chemical Stability (GTR-31472).

IC_{50} values for pantoprazole inhibition of ATP-stimulated acid secretion by pig gastric vesicles at in vitro pH values of 6.1 and 7.4 were 18 and 70 μM, respectively. Similarly, IC_{50} values for omeprazole at in vitro pH values of 6.1 and 7.4 were 4.9 and 25 μM, respectively. Pantoprazole and omeprazole concentrations required to inhibit ATP-stimulated acid secretion were pH-dependent. At pH 6.1 and 7.4, pantoprazole was approximately 3-times less active than omeprazole. Based upon these differences in activity at pH 6.1 and 7.4, pantoprazole may be less likely to transform into the inhibitory chemical species outside the highly acidic parietal cell canaliculi as compared to omeprazole.

Inhibition of Na^+,K^+-ATPase from Dog Kidney in the Presence of Pantoprazole (GTR-31474).

Pantoprazole inhibited Na^+,K^+-ATPase in vitro from dog kidney with an IC_{50} of 177 μM. Pantoprazole had a weak inhibitory effect on Na^+,K^+-ATPase at pH 7.6 as compared to more potent inhibitory effects on H^+,K^+-ATPase, described in earlier studies.

Inhibition of H^+,K^+-ATPase in Pig Stomach Mucosa, Measured as K^+-Dependent p-Nitrophenolphosphatase (K^+pNPPase) Activity in the Presence of Pantoprazole (GTR-31471).

IC_{50} values for pantoprazole inhibition of H^+,K^+-ATPase in pig gastric vesicles, as measured by K^+-dependent p-nitrophenolphosphatase activity, at pH 6.1 and 7.4 were 214 and 324 μM, respectively. K^+-dependent p-nitrophenolphosphate splitting activity of this membrane-bound enzyme does not deliver energy and is not favorable to proton transport. Pantoprazole at pH 6.1 and 7.4 was a weak inhibitor of K^+pNPPase activity.

Inhibition of H^+/K^+-ATPase (Isolated From Fundic Mucosa of Pig Stomach) by Pantoprazole (GTR-31473).

Pantoprazole significantly inhibited H^+/K^+-ATPase (pH 6.1) activity in vitro from pig gastric mucosa (IC_{50} = 3.2 μM).

In Vivo Effects on Gastric Acid Secretion

Rat-Oral

The Effects of Orally Administered Pantoprazole on Basal Acid Secretion in the Conscious Gastric Fistula Rat (GTR-31419).

Pantoprazole administered by the oral route at doses of 0.42, 0.96, 3.83, and 9.59 mg/kg to female Wistar rats with gastric fistulas produced a dose-related inhibition of spontaneous gastric acid secretion. Complete inhibition (96-99%) was obtained with doses