CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-987

PHARMACOLOGY REVIEW(S)

WASH

NDA 20,987

PHARMACOLOGIST'S REVIEW OF NDA 20,987
(Amendments Dated October 1, 1999, October 8, 1999, and October 13, 1999)

Sponsor & Address: Wyeth-Ayerst Research
Philadelphia, PA 19101-82

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

Date of Submission: October 1, 1999
October 8, 1999
October 13, 1999

OCT 15 1999

Date of HFD-180 Receipt: October 4, 1999
October 8, 1999
October 14, 1999

Date of Review: October 14, 1999

Drug: Pantoprazole (PROTONIX™)

Category: Gastric parietal cell H^+,K^+-ATPase inhibitor; Proton Pump Inhibitor

Submission Contents:
1. Draft Report: [redacted]
2. Protocol: Twenty-six Week Oral Gavage Carcinogenicity Study in Male and Female p53(+/-) transgenic mice.

APPEARS THIS WAY
ON ORIGINAL

Carcinogenicity Assessment Committee (CAC/CAC-EC) Cover Sheet
Review of Carcinogenicity Study Design/Dose Selection Proposals

Application (IND/NDA) number: 20,987
Division: Gastrointestinal and Coagulation Drug Products
CAS#:
Drug name: Pantoprazole
Pharmacological Classification: Inhibitor of gastric parietal cell H^+,K^+-ATPase, Proton pump inhibitor
Sponsor/Applicant: Wyeth-Ayerst Research
Sponsor/Applicant contact name: Eleanor Delorme Sullivan, Ph.D.
Sponsor/Applicant telephone and fax number: Phone: 610-902-3710; FAX: 610-964-5973
Date submitted: October 1, 1999, October 8, 1999, and October 13, 1999
45-day date (from submission stamp date): Not Applicable
P/T Reviewer(s): Timothy W. Robison, Ph.D.
Date Review Completed:
Date of CAC review:
CAC members: Joseph DeGeorge, Ph.D. (HFD-024, Chair); Joseph F. Contrera, Ph.D. (HFD-901); Abby Jacobs, Ph.D. (HFD-540); Jasti Choudary, B.V.Sc., Ph.D. (HFD-180, Teamleader); and Timothy Robison, Ph.D. (HFD-180, Reviewer).

Genotoxicity: Pantoprazole was genotoxic in the in vitro human lymphocyte chromosomal aberration assays, the in vitro Chinese hamster ovarian cell/HGPRT forward mutation assay, the in vivo rat liver DNA covalent binding assay, and in one of two mouse micronucleus tests. Pantoprazole was not genotoxic in the Ames test, the in vitro unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the in vitro AS52/GPT mammalian cell-forward gene mutation assay, the vitro thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the in vitro malignant transformation assay with C3H-Mouse M2-fibroblasts and the in vivo rat bone marrow chromosomal aberration assay.

Previous Findings of Carcinogenicity Testing:

In a 24-month carcinogenicity study, Sprague Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare tumors of the stomach produced by treatment included benign adenomatous polyps in the gastric fundus at 200 mg/kg/day, and adenocarcinoma of the gastric fundus at 200 mg/kg/day. Treatment also produced adenocarcinoma of the duodenum at 50 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrence of hepatocellular adenoma, hepatocellular carcinoma, thyroid C-cell adenoma, and malignant neuroendocrine cell tumor was also observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors.

In a 24-month carcinogenicity study, $B6C3F_1$ mice were treated orally with doses of 5 to 150 mg/kg/day. For the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Summary of Proposal for Review:

Species/strain: C57BL/6TacfBR-[KO]p53 mice [p53(+/-) transgenic mice]
Number/sex/dose: 15 mice/sex/group
Route: oral gavage

Doses proposed:		male	female
	Pantoprazole	0, 62.5, 125, & 250 mg/kg/day	0, 62.5, 125, and 250 mg/kg/day
	Omeprazole	0, 150, 360, & 900 mg/kg/day	0, 150, 360, & 900 mg/kg/day
	Lansoprazole	0, 150, 360, & 900 mg/kg/day	0, 150, 360, & 900 mg/kg/day

Basis of dose selection:		
MTD	X	X
AUC ratio		
saturation		
MFD		
PD		
other		

Kinetics submitted:	rodent	human
pharmacokinetics		
metabolism		
protein binding		

Notable design features: The sponsor of pantoprazole is comparing their drug product against marketed drug products, omeprazole (Prilosec®, Astra Pharmaceuticals) and lansoprazole (Prevacid®, TAP Pharmaceuticals). Omeprazole ( ) and lansoprazole ( ) for use as comparators, in the dose range finding study with pantoprazole in C57BL/6TacfBR mice and the proposed 26-week carcinogenicity study with pantoprazole in p53(+/-) transgenic mice, were apparently manufactured and supplied by Byk Gulden in Germany. Differences (i.e., purity, impurities, and excipients) between omeprazole provided by Byk Gulden and Astra Pharmaceuticals, and between lansoprazole provided by Byk Gulden and TAP Pharmaceuticals are unknown.

Summary of Recommendations to CAC

Doses recommended:		male	female
	Pantoprazole	0, 62.5, 125, & 250 mg/kg/day	0, 62.5, 125, and 250 mg/kg/day
	Omeprazole	0, 125, 250, & 500 mg/kg/day	0, 125, 250, & 500 mg/kg/day
	Lansoprazole	0, 125, 250, & 500 mg/kg/day	0, 125, 250, & 500 mg/kg/day

13 PAGE(S) REDACTED

Draft

Protocol: Twenty-six Week Oral Gavage Carcinogenicity Study in Male and Female p53(+/-) Transgenic Mice.

Testing Laboratory:

Histopathology Processing Laboratory:

Necropsy Processing Laboratory:

Protocol: The sponsor has included a protocol for a 26-week carcinogenicity study with pantoprazole in C57BL/6TacfBR-[KO]p53 mice [p53(+/-) mice]. Approved drug products, omeprazole and lansoprazole, will be used as comparators in this study; however, they are manufactured and supplied by Byk Gulden in Germany. High doses selected for pantoprazole, lansoprazole, and omeprazole were 250, 900, and 900 mg/kg/day, respectively. Treatment groups are shown in the table below. There will be 15 mice/sex/group. The control group will receive the vehicle, 0.1 N Na_2CO_3 buffer containing —— Na_2CO_3 and —— $NaHCO_3$, and — methylcellulose with the pH adjusted to a range of 10.5-10.6 using 1 N NaOH or 1 N HCl. The vehicle or drug solution/suspension (pantoprazole is in solution while lansoprazole and omeprazole are in suspension) will be administered by oral gavage using a dose volume of 10 mL/kg. The positive control, p-cresidine, will be administered by oral gavage in corn oil at a dose volume of 10 mL/kg. Body weight will be measured on day 1, once per week through week 13, and every two weeks thereafter. Animals will be observed once per day for clinical signs of toxicity and twice per day for moribundity and mortality. A detailed physical examination of each animal will be performed weekly. Animals that die during the treatment period will be necropsied as soon as possible after being found. Animals that are sacrificed in a moribund condition will be necropsied immediately after sacrifice. At the end of the treatment period, surviving animals will be sacrificed within 24 hr after the last treatment and necropsied. Absolute and relative organ weights will be determined for the brain, heart, liver, kidneys, and testes/ovaries. Organ and tissues from all animals sacrificed at scheduled termination and animals that died or were sacrificed in a moribund condition during the treatment period will be collected and fixed. A portion of grossly observed tumors ≥2 mm will be frozen in liquid nitrogen and stored at -70°C for possible future molecular analysis. Organs and tissue for histopathological examination include: all gross lesions, adrenal glands, brain (cerebrum, cerebellum, and medulla/pons), cecum, cervix, colon, duodenum, esophagus, eyes, femur including marrow and articular surface, gall bladder, Harderian gland, heart and aorta, ileum, jejunum, kidneys, liver, lungs and bronchi, mammary gland, lymph nodes (mandibular and mesenteric), muscle (skeletal), nasal cavity, ovaries, pancreas, parathyroid glands, pituitary gland, prostate, rectum, salivary gland, sciatic nerve, seminal vesicles, skin, spinal cord (cervical, midthoracic, and lumbar), spleen, sternum with bone marrow, stomach, testes/epididymides, thymus, thyroid gland, tongue, trachea, urinary bladder, uterus, and vagina (with cervix). All gross lesions and tissues from all animals in the vehicle-control, positive control, and all pantoprazole treatment groups will be processed and subjected to microscopic examination. For lansoprazole and omeprazole treatment groups, gross lesions and all tissues from the high dose groups animals and animals that died or were sacrificed in a moribund condition during the study period will be processed and subjected to microscopic examination. Target organs identified from the high dose lansoprazole and omeprazole groups and any gross lesions will be evaluated in the mid and low dose groups if necessary to reach a no effect level. Peer review of microscopic findings will be performed. The peer review pathologist, the study pathologist, and a pathologist from Wyeth-Ayerst Research will meet and review all lesions with the intent of both the study

and peer review pathologists indicating what was reviewed and their agreement on final results. For each sex and test article, incidence of mortality and tumors will be compared across dose groups using a Cochran-Armitage trend test and pairwise comparisons of each dose group and control group will be conducted using Fisher's exact test. If intercurrent mortality is observed then trend and pairwise tests for tumor incidence will conducted using Peto Analysis.

Treatment Groups

Group	Treatment	Dose, mg/kg/day
1	Vehicle (control)	0
2	p-Cresidine (Positive Control)	400
3	Pantoprazole	62.5
4	Pantoprazole	125
5	Pantoprazole	250
6	Lansoprazole	125
7	Lansoprazole	360
8	Lansoprazole	900
9	Omeprazole	125
10	Omeprazole	360
11	Omeprazole	900

Evaluation: Based upon results of the 28-day dose range finding study with C57BL/6TacfBR mice, doses recommended for the carcinogenicity study with p53(+/-) transgenic mice are as follows: pantoprazole at 62.5, 125, and 250 mg/kg/day; lansoprazole at 125, 250, and 500 mg/kg/day; and omeprazole at 125, 250, and 500 mg/kg/day. Histopathological evaluation of tissues and gross lesions should be conducted with the vehicle-control group, the positive control group, and low dose, mid dose, and high dose treatment groups for pantoprazole, lansoprazole, and omeprazole as communicated by letter from the Division dated July 12, 1999. Histopathology findings obtained from analyses of tissues by the study pathologist and peer review pathologist should be reported separately as well as the consensus findings from the study, peer review, and Wyeth-Ayerst Research pathologists. We are consulting with FDA statisticians regarding statistical criteria for a positive outcome in the p53(+/-) mouse carcinogenicity study. Per conversation with Dr. Karl Lin, it is anticipated that statistical procedures used with traditional 2-year carcinogenicity studies, as described by the sponsor, will be applied to the p53(+/-) mouse carcinogenicity study. The sponsor of pantoprazole is comparing their drug product against marketed drug products, omeprazole (Prilosec®, Astra Pharmaceuticals) and lansoprazole (Prevacid®, TAP Pharmaceuticals). Omeprazole [redacted] and lansoprazole [redacted], for use as comparators in this study, will be manufactured and supplied by Byk Gulden in Germany. Differences (i.e., purity, impurities, and excipients) between omeprazole provided by Byk Gulden and Astra Pharmaceuticals, and between lansoprazole provided by Byk Gulden and TAP Pharmaceuticals are unknown.

SUMMARY AND EVALUATION

Pantoprazole is an inhibitor of gastric parietal cell H^+,K^+-ATPase proposed for short-term treatment to heal erosive esophagitis in patients with gastroesophageal

reflux disease.

As part of a phase 4 commitment in support of NDA 20,987, the sponsor has been requested to evaluate the carcinogenic potential of pantoprazole in a 26-week carcinogenicity study with p53(+/-) transgenic mice. In the present amendments, the sponsor has submitted a draft report for , and a dose selection proposal and study protocol for a 26-week carcinogenicity study in C57BL/6TacfBR-[KO]p53 mice. The submission dated October 1, 1999 was incomplete as histopathological findings for female treatment groups were not included. The submission dated October 8, 1999 provided histopathology findings for both male and female treatment groups; however, line listings for individual animals were not provided. The submission dated October 13, 1999 provided line listings of histopathology findings for individual animals.

1 PAGE(S) REDACTED

Draft

[ ]

The sponsor has included a study protocol for a 26-week carcinogenicity study with pantoprazole and approved drug products, lansoprazole and omeprazole, in C57BL/6TacfBR-[KO]p53 [p53(+/-) transgenic] mice. High doses selected for pantoprazole, lansoprazole, and omeprazole were 250, 900, and 900 mg/kg/day, respectively. Based upon results of the 28-day dose range finding study with C57BL/6TacfBR mice, doses recommended for the carcinogenicity study with p53(+/-) transgenic mice are as follows: pantoprazole at 62.5, 125, and 250 mg/kg/day; lansoprazole at 125, 250, and 500 mg/kg/day; and omeprazole at 125, 250, and 500 mg/kg/day. Histopathological evaluation of tissues and all gross lesions should be conducted with the vehicle-control group, the positive control group, and low dose, mid dose, and high dose treatment groups for pantoprazole, lansoprazole, and omeprazole as communicated by letter from the Division dated July 12, 1999. Histopathology findings obtained from analyses of tissues by the study pathologist and peer review pathologist should be reported separately as well as the consensus findings from the study, peer review, and Wyeth-Ayerst Research pathologists. Approved drug products, omeprazole and lansoprazole, will be used as comparators in this study; however, they are manufactured and supplied by Byk Gulden in Germany. Differences (i.e., purity, impurities, and excipients) between omeprazole provided by Byk Gulden and Astra Pharmaceuticals, and between lansoprazole provided by Byk Gulden and TAP Pharmaceuticals are unknown.

Recommendation:

Doses recommended for the 26-week carcinogenicity study with p53(+/-) transgenic mice are as follows:
Pantoprazole: 62.5, 125, and 250 mg/kg/day
Lansoprazole: 125, 250, and 500 mg/kg/day
Omeprazole: 125, 250, and 500 mg/kg/day

1. For a timely review of studies and protocols, it is recommended that reports be complete and accurate. The submission dated October 1, 1999 contained no histopathology findings for female mice. Further, this submission contained inaccuracies such as the reported incidence of fundic gland ectasia for male treatment groups in tables accompanying discussion of histopathology data. The submission dated October 8, 1999 provided histopathology findings for both male and female treatment groups; however, line listings for individual animals were not provided. It is not possible to relate clinical chemistry findings of elevated creatinine, blood urea nitrogen, and aspartate aminotransferase activity in individual animals with corresponding histopathological findings. Inaccuracies noted in the submission dated October 1, 1999 were not corrected in the submission dated October 8, 1999.

2. For the 26-week carcinogenicity study in p53(+/-) transgenic mice, histopathological evaluation of tissues and all gross lesions should be conducted with the vehicle-control

group, the positive control group, and low dose, mid dose, and high dose treatment groups for pantoprazole, lansoprazole, and omeprazole as communicated by letter from the Division dated July 12, 1999. Histopathology findings obtained from analyses of tissues by the study pathologist and peer review pathologist should be reported separately as well as the consensus findings from the study, peer review, and Wyeth-Ayerst Research pathologists.

3. Approved drug products, omeprazole and lansoprazole, will be used as comparators in the 26-week carcinogenicity study with pantoprazole in p53(+/-) transgenic mice; however, they are manufactured and supplied by Byk Gulden in Germany. Differences (i.e., purity, impurities, and excipients) between omeprazole provided by Byk Gulden and Astra Pharmaceuticals, and between lansoprazole provided by Byk Gulden and TAP Pharmaceuticals are unknown. The sponsor should be requested to consider having omeprazole and lansoprazole manufactured by Byk Gulden in Germany compared with omeprazole manufactured by Astra Pharmaceuticals and lansoprazole manufactured by TAP Pharmaceuticals by an independent analytical testing laboratory to determine potential differences in purity, impurities, and excipients.

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

10-14-99
Date

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

/S/
10/15/99

APPEARS THIS WAY
ON ORIGINAL

WALSH

NDA 20,987

AUG 13 1999

PHARMACOLOGIST'S REVIEW OF NDA 20,987
(Amendment Dated June 4, 1999)

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

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

Date of Submission: June 4, 1999

Date of HFD-180 Receipt: June 7, 1999

Date of Review: August 13, 1999

Drug: Pantoprazole (PROTONIX™)

Category: Gastric parietal cell H^+,K^+-ATPase inhibitor; Proton Pump Inhibitor.

Submission Contents:

Wyeth-Ayerst Research and Byk Gulden held a meeting on December 19, 1998 in Pearl, NY, at their own initiative, to conduct a histopathologic rediagnosis of stomach tumors and metastases that were considered to be rare or unusual from selected Sprague-Dawley rats of the two-year carcinogenicity study (See review of Amendment dated January 28, 1998). During ——— meeting on May 27, 1999, a question arose regarding the statistical reanalysis of pancreatic tumors as a result of the reclassification of metastases.

In the original report of the Sprague-Dawley rat carcinogenicity study (GTR-31282), the incidence of tumor findings in the pancreas displayed no relationship to pantoprazole treatment as shown in the table below.

Original reported incidence of pancreatic tumor finding for Sprague-Dawley rats that received pantoprazole by the oral route at doses of 0, 0.5, 5, 50, and 200 mg/kg/day for ≤2 years.

Tumor findings	0 mg/kg/day		0.5 mg/kg/day		5 mg/kg/day		50 mg/kg/day		200 mg/kg/day	
	M	F	M	F	M	F	M	F	M	F
Islet cell adenoma	6	0	3	2	1	0	4	1	0	2
Islet cell carcinoma	2	0	0	0	1	0	2	0	1	0
Islet cell adenoma + carcinoma	8	0	3	2	2	0	6	1	1	2
Acinar cell adenoma	4	0	2	0	1	0	2	0	1	1
Acinar cell carcinoma	0	1	0	0	0	0	0	0	0	0
Acinar cell adenoma + carcinoma	4	1	2	0	1	0	2	0	1	1

Histopathologic rediagnosis of stomach tumors and metastases from selected Sprague-Dawley rats of the two-year carcinogenicity study by Wyeth-Ayerst Research and Byk Gulden was evaluated by [redacted] (See Memorandum dated June 25, 1999). Results of tissue rediagnoses are shown in the table below.

Sprague-Dawley Rat Study

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

For animals #4718 (5 mg/kg/day, male) and #4997 (200 mg/kg/day, male), tumors found in the liver were rediagnosed as metastatic islet-cell carcinomas from the pancreas. It should be noted that the original study report for each animal listed no tumor findings for the pancreas.

Given the reported high incidence of islet cell adenoma + carcinoma in the pancreas for control animals, the tissue rediagnosis had no effect on the conclusion that there were no treatment-related tumor findings in pancreas for the Sprague-Dawley rat carcinogenicity study with pantoprazole.

SUMMARY AND EVALUATION

Wyeth-Ayerst Research and Byk Gulden held a meeting on December 19, 1998 in Pearl, NY, at their own initiative, to conduct a histopathologic rediagnosis of stomach tumors and metastases that were considered to be rare or unusual from selected Sprague-Dawley rats of the two-year carcinogenicity study (See review of Amendment dated January 28, 1998). During the _____ _____ a question arose regarding the statistical reanalysis of pancreatic tumors as a result of the reclassification of metastases.

Histopathologic rediagnosis of stomach tumors and metastases from selected Sprague-Dawley rats of the two-year carcinogenicity study by Wyeth-Ayerst Research and Byk Gulden was evaluated by _____ (See Memorandum dated June 25, 1999). For animals #4718 (5 mg/kg/day, male) and #4997 (200 mg/kg/day, male), tumors found in the liver were rediagnosed as metastatic islet-cell carcinomas from the pancreas. It should be noted that the original study report for each animal listed no tumor findings for the pancreas. Given the reported high incidence of islet cell adenoma + carcinoma in the pancreas for control animals, the tissue rediagnoses had no effect on the conclusion that there were no treatment-related tumor findings in pancreas for the Sprague-Dawley rat carcinogenicity study with pantoprazole.

RECOMMENDATIONS:

None.

/S/

Timothy W. Robison, Ph.D. 8-13-99
Date

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

/S/ 8/13/99

R/D Init.: J. Choudary 8/13/99

TWR/hw/8/13/99

(Wabot)

NDA 20,987

PHARMACOLOGIST'S REVIEW OF NDA 20,987
(Amendment Dated June 21, 1999)

Sponsor & Address: Wyeth-Ayerst Research
Philadelphia, PA 19101-82

JUL - 6 1999

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

Date of Submission: June 21, 1999

Date of HFD-180 Receipt: June 22, 1999

Date of Review: July 6, 1999

Drug: Pantoprazole (PROTONIX™)

Category: Gastric parietal cell H^+,K^+-ATPase inhibitor; Proton Pump Inhibitor.

Submission Contents:

In [redacted] As part of a phase 4 commitment in support of NDA 20,987, the sponsor has been requested to conduct a 26-week carcinogenicity study with pantoprazole in p53(+/-) mice. The sponsor in the present submission has provided a draft protocol for a 26-week carcinogenicity study in p53(+/-) mice. In addition, questions related to conduct of the carcinogenicity study were included.

Carcinogenicity Assessment Committee (CAC/CAC-EC) Cover Sheet
Review of Carcinogenicity Study Design/Dose Selection Proposals

Application (IND/NDA) Number: 20,987
Division: Gastrointestinal and Coagulation Drug Products
CAS#:
Drug Name: Pantoprazole
Pharmacological Classification: Inhibitor of gastric parietal cell H^+,K^+-ATPase, Proton pump inhibitor.
Sponsor/Applicant: Wyeth-Ayerst Research
Sponsor/Applicant Contact Name: Eleanor Delorme Sullivan, Ph.D.
Sponsor/Applicant Telephone and Fax Number: Phone: 610-902-3710; FAX: 610-964-5973
Date Submitted: June 21, 1999
45-Day Date (from submission stamp date): Not applicable
P/T Reviewer(s): Timothy W. Robison, Ph.D.
Date Review Completed: July 6, 1999
Date of CAC review:
CAC members: Joseph DeGeorge, Ph.D. (HFD-024, Chair); Jasti Choudary, B.V.Sc., Ph.D. (HFD-180, Teamleader), and Timothy Robison, Ph.D. (HFD-180, Reviewer).

Summary of Proposal for Review:

Species/Strain: C57BL/6TacfBR-[KO]p53N5 Heterozygous mice
Number/Sex/Dose: 15 mice/sex/group
Route: Oral gavage

		Male	Female
Doses Proposed:	Pantoprazole Omeprazole Lansoprazole	[	]

Basis of Dose Selection: Not Stated.

MTD	____	____
AUC ratio	____	____
saturation	____	____
MFD	____	____
PD	____	____
other	____	____

Kinetics Submitted:	Rodent	Human
pharmacokinetics	X	X
metabolism	X	X
protein binding	X	X

Notable Design Features: None.

1 PAGE(S) REDACTED

Draft

Questions regarding the conduct of the 26-week carcinogenicity study are addressed in a point-by-point manner below. The sponsor's questions are enclosed within quotations followed by a response. An evaluation of the draft protocol for a 26-week carcinogenicity study in p53(+/-) mice follows responses to questions.

"**1.** In reference to the proposed 26-week week mouse study, should histopathological evaluations be conducted for **all tissues** or for **only the specific target organs.**"

Response: Given the genotoxic findings with pantoprazole, histopathological evaluation should be conducted with all tissues. Further, tissues for histopathological analysis should be in accordance with the [redacted] Final Protocol dated June 10, 1997 entitled "Twenty-Six Week Carcinogenicity Study in $p53^{+/-}$ Heterozygous Mice". Histopathological evaluation should be conducted with gross lesions and tissues listed below. All tissues should be preserved, processed, and stained for histopathological examination. It should be noted that histopathological evaluation of tissues and gross lesions should be conducted with the vehicle-control group, the positive control group, and low dose, mid dose, and high dose treatment groups for pantoprazole and each reference drug in the 26-week carcinogenicity study.

Tissues for Histopathological Evaluation: adrenal glands, aorta, bone marrow (femur), bone marrow (sternum), brain (forebrain, midbrain, hindbrain), epididymides, esophagus, eyes, gall bladder, harderian/lacrimal glands, heart, large intestines (3 sites), small intestines (3 sites), kidneys, liver, lungs, mesenteric lymph nodes, submaxillary lymph nodes, mammary glands, nasal cavity, ovaries, pancreas, parathyroid glands (if possible), pituitary gland, prostate gland, salivary gland, sciatic nerve, seminal vesicle, skeletal muscle, skin, spinal cord, spleen, stomach (glandular and nonglandular), testes, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina-cervix.

"**2.** Since it will be important to establish statistical criteria for a positive outcome (as defined by the Agency) prior to study completion, we request your feedback concerning the statistical criteria to be utilized."

Response: We are consulting with FDA statisticians regarding statistical criteria for a positive outcome in the p53(+/-) mouse carcinogenicity study. Per conversation with Dr. Karl Lin, it is anticipated that statistical procedures used with traditional 2-year carcinogenicity studies will be applied to the p53(+/-) mouse carcinogenicity study.

"**3.** Wyeth has compiled historical data from several mouse studies for the PPIs to be compared in the 26-week mouse study. The data are summarized in the table below. To expedite the initiation of the 26-week mouse study, could these historical data be utilized to select doses in lieu of the conduct of a separate dose range study?"

Exposure Data in Mice for Pantoprazole, Omeprazole, and Lansoprazole.

Compound	Mouse Strain	Top Dose mg/kg/day	AUC[a] mg.hr/L
Pantoprazole	B6C3F1	150	15
Omeprazole	CD-1	140/170[b]	0.56
Lansoprazole	CD-1	50	-
	CD-1	300	-
	CD-1	600	2.36

a. average of male and female mice.
b. reduced at week 66.

Response: The historical data described in the table is not appropriate for use in dose selections with pantoprazole and the two approved reference drugs, omeprazole and lansoprazole, particularly given the use of different strains of mice. Further, the lansoprazole dose of 600 mg/kg/day in the two-year carcinogenicity study with CD-1 mice was associated with excessive mortality. A four week dose range finding toxicity study in C57BL/6 mice (i.e., wild strain of p53(+/-) mice) should be conducted for pantoprazole and each reference drug. There should be 5 to 6 mice/sex/group. Animals should be observed daily for clinical signs of toxicity and mortality. Body weight and food consumption should be measured pretest and once weekly thereafter until necropsy. Necropsy examinations should be performed on all animals. Terminal body weights should be measured for all animals excluding early death/early sacrifice. Blood for hematology and serum biochemistry should be collected. Organ weights should be determined for the brain, heart, kidneys, liver, gonads (testes and ovaries) of all animals excluding early deaths/early sacrifices. For histopathology, gross lesions and tissues for all groups as listed under Question 1 should be preserved in 10% neutral buffered formalin, processed, and stained for examination. Representative sections of all tissues and any gross lesions from all mice in the vehicle-control group and low dose, mid dose, and high dose treatment groups for pantoprazole and each reference drug should be submitted to histopathological evaluation. All operations and methods pertaining to this study should be performed according to Good Laboratory Practices. A maximum tolerated dose (MTD) should be identified for pantoprazole and each reference drug based upon observed dose-limiting toxicity (i.e., 10% decrease in body weight gain relative to controls, histopathological lesions).

"4. If extrapolation from the historical data is not feasible, would clinical signs including body weight gain, food consumption, clinical chemistry, and hematology data be considered sufficient for the selection of maximum tolerated doses (MTDs)?

Response: Organ/tissue histopathology is an integral part of a dose range finding toxicity study. Clinical signs, body weight gain, food consumption, clinical chemistry, and hematology are not sufficient without histopathopathological evaluation of tissues. Representative sections of all tissues and any gross lesions from all mice in the vehicle-control group and low dose, mid dose, and high dose treatment groups for pantoprazole and each reference drug should be submitted to histopathological evaluation.

SUMMARY AND EVALUATION

Pantoprazole is an inhibitor of gastric parietal cell H^+,K^+-ATPase proposed for short-term treatment to heal erosive esophagitis in patients with gastroesophageal reflux disease. In [redacted] pantoprazole was determined to be genotoxic and carcinogenetic. As part of a phase 4 commitment in support of NDA 20,987, the sponsor has been requested to evaluate the carcinogenic potential of pantoprazole in a 26-week carcinogenicity study with p53(+/-) transgenic mice.

The sponsor has submitted a draft protocol for a 26-week carcinogenicity study with pantoprazole in p53(+/-) transgenic mice. Two approved reference drugs, omeprazole and lansoprazole, will be included in the study as comparators. Dose selections for pantoprazole as well as each reference drug should be based upon 4-week dose range finding studies using C57BL/6 mice (i.e., wild strain of p53(+/-) mice). A maximum tolerated dose (MTD) should be identified for pantoprazole and each reference drug based upon dose-limiting toxicity (i.e., 10% decrease in body weight gain relative to controls, histopathological lesions). It is not appropriate to use historical data with pantoprazole and approved reference drugs obtained in different mouse strains for selection of doses in the 26-week carcinogenicity study with p53(+/-) mice.

For the 26-week carcinogenicity study in p53(+/-) mice, tissues and gross lesions for histopathological evaluation should conform to the —— Final Protocol dated June 10, 1997. Representative sections of all tissues and any gross lesions from all mice in the vehicle-control group, positive control group, and low dose, mid dose, and high dose groups for pantoprazole and each reference drug should be submitted to histopathological evaluation.

RECOMMENDATION: The following information should be communicated to the sponsor.

1. A four week oral dose range finding toxicity study in C57BL/6 mice (i.e., wild strain of p53(+/-) mice) should be conducted for pantoprazole and approved reference drugs, omeprazole and lansoprazole. There should be 5 to 6 mice/sex/group. Pantoprazole and each reference drug should be administered by oral gavage in alkaline solution to prevent acid-induced drug degradation in the stomach. Animals should be observed daily for clinical signs of toxicity and mortality. Body weight and food consumption should be measured pretest and once weekly thereafter until necropsy. Necropsy examinations should be performed on all animals. Terminal body weights should be measured for all animals excluding early death/early sacrifice. Blood for hematology and serum biochemistry should be collected. Organ weights should be determined for the brain, heart, kidneys, liver, gonads (testes and ovaries) of all animals excluding early deaths/early sacrifices. For histopathology, any gross lesions and tissues as listed under Recommendation #2 should be preserved, processed, and stained for examination. Representative sections of all tissues and any gross lesions from all mice in the vehicle-control group and low dose, mid dose, and high dose treatment groups for pantoprazole and each reference drug should be submitted to histopathological evaluation. All operations and methods pertaining to this study should be performed according to Good Laboratory Practices. A maximum tolerated dose (MTD) should be identified for pantoprazole and each reference drug based upon observed dose-limiting toxicity (i.e., 10% decrease in body weight gain relative to controls, histopathological lesions).

2. Tissues for histopathological analysis should be in accordance with the [redacted] Final Protocol dated June 10, 1997 entitled "Twenty-Six Week Carcinogenicity Study in $p53^{+/-}$ Heterozygous Mice". Representative sections of all tissues and any gross lesions as listed below from all mice in the vehicle-control group, positive control group, and low dose, mid dose, and high dose groups for pantoprazole and each reference drug should be submitted to histopathological evaluation. All tissues should be preserved, processed, and stained for histopathological examination.

Tissues for Histopathological Evaluation: adrenal glands, aorta, bone marrow (femur), bone marrow (sternum), brain (forebrain, midbrain, hindbrain), epididymides, esophagus, eyes, gall bladder, harderian/lacrimal glands, heart, large intestines (3 sites), small intestines (3 sites), kidneys, liver, lungs, mesenteric lymph nodes, submaxillary lymph nodes, mammary glands, nasal cavity, ovaries, pancreas, parathyroid glands (if possible), pituitary gland, prostate gland, salivary gland, sciatic nerve, seminal vesicle, skeletal muscle, skin, spinal cord, spleen, stomach (glandular and nonglandular), testes, thymus, thyroid gland, trachea, urinary bladder, uterus, and vagina-cervix.

/S/
Timothy W. Robison, Ph.D. — 7-6-99 Date

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

/S/ 7/6/99

R/D Init.: J. Choudary 7/2/99

TW:R/hw/7/6/99

APPEARS THIS WAY
ON ORIGINAL

WALSH

MEMORANDUM

(Review)

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

DATE: June 25, 1999

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

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

TO: NDA 20,987

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

APPEARS THIS WAY
ON ORIGINAL

Sprague-Dawley Rat Study

Animal # & Sex	Dose mg/kg/day	Original Finding by	Present Sponsor's (Wyeth-Ayerst) Changed Diagnoses	NCTR Sponsored Pathologists Diagnoses
4718 (male)	5	Metastasis of NE-cell tumor in liver with no primary site	Pancreatic Islet cell carcinoma	Islet cell carcinoma, beta cell
4997 (male)	200	"	"	"
4883 (male)	50	"	Anaplastic sarcoma	Sarcoma, nos
5001 (male)	200	Adenomatous polyp-stomach	Adenomatous polyp, stomach	Adenomatous polyp, stomach
5055 (male)	200	"	"	"
5122 (female)	200	"	"	"
5108 (female)	200	NE-cell tumor-stomach & Metastases (lung, liver, duodenum, mesenteric lymph node & pancreas)	NE-cell tumor-stomach & metastases	Neuroendocrine cell tumor, malignant, Stomach with metastases to other organs. **Adenomatous polyp-stomach**
4906 (male)	50	Adenocarcinoma of stomach (pyloric region)	Adenocarcinoma-duodenum	Adenocarcinoma-duodenum
5[illegible] (female)	200	NE-cell tumor-stomach & Lymph node metastasis	Pancreatic acinar cell carcinoma	**Adenocarcinoma-stomach.** Lymph node metastasis
5100 (female)	200	Chief cell adenocarcinoma-stomach NE-cell tumors-stomach	NE-cell tumors with areas of chief cell like differentiation or Chief cell adenocarcinoma with features of neuroendocrine cell differentiation	Mixed tumor-malignant NE-cell tumor-stomach & **Adenocarcinoma-stomach**

Fischer Rat Study

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

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