The "Carcinogenesis, Mutagenesis, Impairment of Fertility" subsection of the "PRECAUTIONS" section is changed to reflect the outcome of the histopathology examination by the NCTR sponsored pathologists. The changed labeling is reproduced below.

"PRECAUTIONS

Carcinogenesis, Mutagenesis, Impairment of Fertility

/S/ 6/28/99
Jasti B. Choudary, B.V.Sc., Ph.D.

ATTACHMENT: Fax Memorandum Dated June 24, 1999 from

cc:
NDA
HFD-180
HFD-181/CSO/Ms. Walsh
HFD-180/Dr. Choudary
HFD-180/Dr. Robison
HFD-180/Dr. Gallo-Torres
HFD-180/Dr. Talarico
HFD-024/Dr. DeGeorge
HFD-024/Ms. Seifried

JBC/hw/6/28/99

Walsh

NDA 20,987

PHARMACOLOGIST'S REVIEW OF NDA 20,987
(Amendment Dated June 2, 1999)

JUN 18 1999

Sponsor & Address: Wyeth-Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-82

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

Date of Submission: June 2, 1999

Date of HFD-180 Receipt: June 3, 1999

Date of Review: June 18, 1999

Drug: Pantoprazole (PROTONIX™)

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

Submission Contents:

Correspondence from the sponsor regarding issues raised [redacted] For each issue, the sponsor's position is summarized within quotations followed by an evaluation of each position.

1. Thyroid tumorigenesis observed in the Sprague-Dawley rat carcinogenicity study.

Sponsor's Position: The sponsor has included reviews of thyroid function studies (GTR-31307, GTR-31304, GTR-31720, GTR-31306, and GTR-31719) by [redacted] Conclusions of his reviews are enclosed within quotations. "Female rats received either pantoprazole, omeprazole, or lansoprazole at doses of 5, 50, or 300 mg/kg/day for 1 week. Pantoprazole at 300 mg/kg/day induced catabolism of thyroid hormones and increased biliary excretion of thyroid hormone-glucuronide. The effects of pantoprazole were less than omeprazole or lansoprazole. No change in T_3 or T_4 levels was observed with pantoprazole treatment. Pantoprazole was administered to rats at doses ranging from 10 to 200 mg/kg/day for 4 weeks. Only the high dose of 200 mg/kg/day was found to increase UDP-glucuronyl transferase activity on day 28; however, no changes in T_4 or TSH levels were observed. In bile duct-cannulated female rats, treatment with pantoprazole at 300 mg/kg/day for 4 weeks was found to increase biliary excretion of T_4 in a similar manner to phenobarbital at 75 mg/kg/day. Female rats received pantoprazole at doses of 0, 50, 200, and 500 mg/kg/day for 4 weeks. Only the high dose of 500 mg/kg/day produced a statistically significant

decrease in T_3 levels and a statistically significant increase in TSH levels. The low and mid doses produced similar trends; although, changes were not statistically significant. No change in T_4 levels was observed any dose. Changes produced by pantoprazole at 500 mg/kg/day were greater than those produced by phenobarbital at 75 mg/kg/day. Pantoprazole administered to female rats at a dose of 200 mg/kg/day for 2 weeks had no effect on thyroid peroxidase activity."

Evaluation: The sponsor has contended in previous correspondence that thyroid tumors were generated in response to an imbalance of thyroid metabolism (i.e., Thyroid stimulating hormone-driven); although, no such relationship was proposed in the present submission. TSH-driven thyroid follicular hypertrophy and hyperplasia can result from either direct inhibition of thyroid peroxidase (which incorporate iodine into T_4 and T_3) or indirectly through metabolism (i.e., glucuronide conjugation) and/or excretion (i.e., biliary), and receptor-mediated effects at hypothalamic and pituitary levels. In the Sprague-Dawley rat carcinogenicity study, pantoprazole produced significant increases in the incidences of thyroid follicular cell adenomas and carcinomas in both male and female rats, which were not observed in Sprague-Dawley rat carcinogenicity studies with omeprazole and lansoprazole. In a 4-week study of thyroid function with Sprague-Dawley rats, pantoprazole at 500 mg/kg/day decreased T_3 levels by 29-40% of the control and increased TSH levels by 2- to 3-fold; however, at 200 mg/kg/day, the highest dose used in the carcinogenicity study, there were no changes in T_3 or TSH levels. T_4 levels were unaffected by pantoprazole at 200 or 500 mg/kg/day **(It should be noted that author of the sponsor's report, ——————— stated that "the lack of a decrease in T_4 levels is a bit unusual for a compound that acts by this mechanism").** In a 2-week study with Sprague-Dawley rats, pantoprazole at 200 mg/kg/day, the highest dose used in the carcinogenicity study with Sprague-Dawley rats, had no effect on thyroid peroxidase activity and subsequent biosynthesis of thyroid hormones; although, uptake of iodine was enhanced as compared to the control following TSH stimulation. Following treatment of Sprague-Dawley rats with either pantoprazole, lansoprazole, or omeprazole at doses of 5, 50, or 300 mg/kg/day for 1 week, significant induction of hepatic UDP-glucuronyl transferase (UDPGT) activity was observed with all three agents; however, the induction of UDPGT found with pantoprazole was smaller than that observed with either omeprazole or lansoprazole. Biliary excretion of [^{125}I]thyroxine (T_4) was significantly increased by the treatment of rats with all three agents; however, the increased biliary excretion of radiolabeled T_4 found with pantoprazole was much smaller than that observed with omeprazole or lansoprazole. Thus, the effects of pantoprazole on induction of hepatic UDPGT activity and thyroid hormone metabolism were smaller than those observed for omeprazole or lansoprazole; however, in 2-year carcinogenicity studies, thyroid tumor were only observed with pantoprazole. Follicular cell hypertrophy but not hyperplasia was observed in the 1-year chronic toxiciology study. Thus, thyroid tumors observed in pantoprazole-treated rats cannot be explained by an imbalance of thyroid hormone metabolism (i.e., TSH-driven). Pantoprazole has been shown to be clastogenic and mutagenic, which may potentially explain development of thyroid tumors. **(It should be noted that author of the sponsor's report, ——————— , drew no conclusions regarding the mechanism of pantoprazole-induced thyroid tumorigenesis).**

2. Granulocytic leukemia was observed in 1 male rat at 15 mg/kg/day (#83) and 2 male rats at 50 mg/kg/day (#41 and #410) from the Fischer 344 rat carcinogenicity study.

Sponsor's Position: "The sponsor contends that the low incidence of granulocytic leukemia was likely a misdiagnosis of Fischer rat large granular lymphocyte (LGL) leukemia, also known as mononuclear cell leukemia, which predominates in male rats of this strain. To further assess this issue, the sponsor proposes to provide the FDA with histopathology slides and paraffin blocks from the 3 animals in question, along with histopathology slides from an additional 9 male rats from the same study diagnosed with LGL leukemia. Thus, the sponsor is proposing to provide histopathology slides from the 3 animals in question, as well as from 4 high-dose, 2 mid-dose, and 3 control animals that had diagnoses of LGL leukemia."

Evaluation: Granulocytic leukemia is a rare tumor for Fischer 344 rats [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)]. LGL leukemia is a common finding in both male and female Fischer 344 rats. High mortality rates in the female vehicle-control and treatment groups during the first year of treatment were possibly responsible for the lower incidence of LGL leukemia as compared to male rats as well as the lack of finding of granulocytic leukemia in female treatment groups (see table below with incidences of granulocytic and LGL leukemias in the Fischer rat carcinogenicity study). If misdiagnoses were responsible for the findings of granulocytic leukemia in the male mid and high dose treatment groups, then one might have expected these misdiagnoses to have occurred in other male rat groups, given the high prevalence of LGL leukemia. Providing histopathology slides as well as tissue paraffin blocks from the 3 animals in question to Dr. William Witt at the National Center for Toxicological Research for analysis, should provide some resolution as to the type of leukemia that occurred in these animals. However, the sponsor's proposal to provide histopathology slides from an additional 9 male rats from the same study diagnosed with LGL leukemia is somewhat questionable. For purposes of not introducing any potential bias into the analysis, slides from the 3 male rats diagnosed with granulocytic leukemia as well as all male rats diagnosed with LGL leukemia should be provided to Dr. Witt. Slides should be examined under blinded conditions.

Incidence of granulocytic leukemia and large granular lymphocyte (LGL) leukemia at doses of 0 (untreated control, UC), 0 (vehicle-control, VC), 5, 15, and 50 mg/kg/day in the Fischer 344 rat carcinogenicity study with pantoprazole.

Hematopoietic System	Sex	0 (UC)	0 (VC)	5	15	50
Granulocytic leukemia	Male	0	0	0	1	2
	Female	0	0	0	0	0
LGL leukemia	Male	19	13	16	7	13
	Female	7	3	2	5	1

3. Reanalysis of tumor findings in the stomach, lymph nodes, and liver from the Sprague-Dawley rat carcinogenicity study.

Sponsor's Position: "Wyeth-Ayerst Research and Byk Gulden held a meeting on December 19, 1998 in Pearl, NY, at their own initiative, to conduct a histopathologic re-evaluation of specific tumors that were considered to be rare or unusual from selected Sprague-Dawley rats of the two-year carcinogenicity study. Results of this reanalysis are shown in the table below. Based upon tumor reanalyses described in the table below, the sponsor will submit updated electronic data for the Sprague-Dawley rat carcinogenicity study as well as a statistical reanalysis of pancreatic tumor data."

HISTOPATHOLOGIC PEER REVIEW OF SPECIFIC TUMORS IN RATS FROM SPRAGUE-DAWLEY CARCINOGENICITY STUDY

Organ Animal No.	Dosage (mg/kg/day) and Sex	Original Report in NDA (January 1995)[a]	Report of Special Staining Morphology in NDA (July 1995)[b]	Consensus of Histopathologic Peer Review December 1998 (To FDA January 28, 1999)
Stomach				
5001	200 M	Adenomatous polyps	NA	Adenomatous polyps
5055	200 M	Adenomatous polyps	NA	Adenomatous polyps
5122	200 F	Adenomatous polyps	NA	Adenomatous polyps
5100	200 F	Chief-cell adenocarcinoma and NE-cell tumor	NA	NE-cell tumor with areas of chief-cell-like differentiation
4998	50 M	Adenocarcinoma at gastroduodenal junction (pyloric region)	NA	Adenocarcinoma of Brunner's glands of duodenum
Stomach and Lymph Node				
5108	200 F	NE-cell tumor in stomach and metastases (lung, liver, duodenum, mesenteric lymph node, and pancreas)	NE-cell tumor in stomach and metastases	NE-cell tumor in stomach and metastases
4870	50 M	NE-cell tumor in stomach and lymph node metastasis (near pancreas)	Pancreatic acinar-cell carcinoma	Pancreatic acinar-cell carcinoma
5070	200 F	NE-cell tumor in stomach and lymph node metastasis (near pancreas)	Pancreatic acinar-cell carcinoma	Pancreatic acinar-cell carcinoma
Liver				
4718	5 M	Metastasis of NE-cell tumor in liver with no primary site	Pancreatic islet-cell carcinoma	Pancreatic islet-cell carcinoma
4997	200 M	Metastasis of NE-cell tumor in liver with no primary site	Pancreatic islet-cell carcinoma	Pancreatic islet-cell carcinoma
4883	50 M	Metastasis of NE-cell tumor in liver with no primary site	Anaplastic sarcoma	Anaplastic sarcoma

a: GTR-31282
b: GTR-31279
F – Female; GTR = General Technical Report; M = Male; No. = Number; NA = Not applicable; NE = Neuroendocrine

APPEARS THIS WAY
ON ORIGINAL

Evaluation: Reclassification of tumors and any subsequent statistical reanalysis of tumors should await independent verification of tumor reclassification by Dr. William Witt at the National Center for Toxicological Research. Comments on tumor reanalysis are listed below. For more detailed comments regarding tumor reanalysis, see review of the Amendment submitted on January 28, 1999 (Document Room Date June 10, 1999).

Animal numbers 5001 (200 mg/kg/day, male), 5055 (200 mg/kg/day, male), and 5122 (200 mg/kg/day, female) were identified with findings of typical adenomatous polyps in the glandular stomach in the original report. There were no changes following reanalysis.

Animal number 5100 (200 mg/kg/day, female) was identified with separate findings in the fundus of a malignant chief cell adenocarcinoma and multiple malignant neuroendocrine (NE) cell tumors in the original report. The original diagnoses of both NE cell-tumor and chief-cell adenocarcinoma (merging or collision) were considered reasonable, although debatable, diagnoses. Reanalysis led to a reclassification of the chief cell adenocarcinoma as a NE-cell tumor with areas of chief-cell-like differentiation. The original diagnosis and the reanalysis appear to agree that there was a merging or collision of NE-cells and chief-cells. The original tumor diagnosis appears unchanged; although, different terminology is used to describe the finding.

Animal number 4908 (50 mg/kg/day, male) was identified with a malignant adenocarcinoma in the pyloric region at the gastroduodenal junction in the original report. Reanalysis suggested that this tumor was a primary tumor of duodenum rather than stomach and represented an adenocarcinoma of Brunner's glands. In the original report from ———————— , the only neoplastic finding listed for the small intestine was a malignant histiocytic sarcoma in the duodenum. The validity of the reanalysis is somewhat questionable.

Animal number 5108 (200 mg/kg/day, female) was identified with NE-cell tumors in the stomach with metastases in lung, liver, duodenum, mesenteric lymph node, and pancreas. There were no changes following reanalysis.

Animal number 4870 (50 mg/kg/day, male) was identified with a malignant neuroendocrine cell tumor (metastatic site) in a lymph node adjacent to the pancreas) and a malignant neuroendocrine cell tumor in the fundus (metastasizing). Both tumors were reclassified as acinar-cell carcinomas of the pancreas after reanalysis. The original study report listed no abnormalities for the pancreas. It is difficult to understand how these neuroendocrine cell tumors were reclassified as acinar-cell carcinomas of the pancreas in the apparent absence of a primary acinar-cell carcinoma in the pancreas.

Animal number 5070 (200 mg/kg/day, female) was identified with a malignant neuroendocrine cell tumor in a lymph node near the pancreas (metastatic site) and multiple, malignant neuroendocrine cell tumors in the fundus (metastasizing) in the original report. Both tumors were reclassified as acinar-cell carcinomas of the pancreas following reanalysis. However, use of special stains and immunohistochemistry were inconclusive with regard to identification of the neoplastic findings as either neuroendocrine cell tumors or acinar-cell carcinomas. Reanalysis made no definitive identification of these tumors.

Animal numbers 4718 (5 mg/kg/day, male) and 4997 (200 mg/kg/day, male) were both reported with a finding of a malignant NE-cell tumor in the liver (site of origin not determined) in the original report. These tumors were subsequently diagnosed as metastatic islet-cell carcinomas following reanalysis. The original study report listed no abnormalities for the pancreas for either animal. It is difficult to understand how these neuroendocrine cell tumors were reclassified as metastatic islet-cell carcinomas from pancreas in the apparent absence of a primary islet-cell carcinoma in the pancreas.

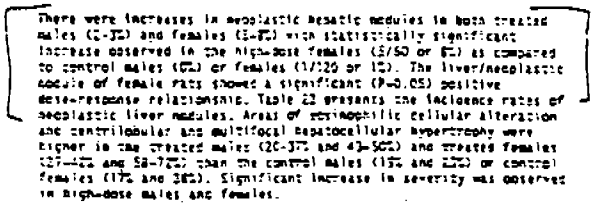
Animal number 4883 (50 mg/kg/day, male) was reported listed a finding of a malignant NE-cell tumor in the liver (site of origin not determined). The tumor was reclassified as an anaplastic sarcoma following reanalysis. Anaplastic sarcomas in rat liver appears to be rare (In: Pathobiology of Tumors in Laboratory Animals. Editor: V.S. Turusov. International Agency for Research on Cancer Animals. Lyon. 1987, Part 2, Pages 48-50).

4. Incidence of liver tumors in Sprague-Dawley rat carcinogenicity studies with omeprazole and lansoprazole.

Sponsor's Position: "The sponsor presented data regarding the incidences of liver tumors in Sprague-Dawley rat carcinogenicity studies with omeprazole and lansoprazole as shown below. The source of liver tumor incidence for omeprazole was the FDA pharmacology and toxicology review and an addendum by the supervisory pharmacologist Dr. J. Choudary (NDA 19,810). The source of liver tumor incidence for lansoprazole was the FDA pharmacology and toxicology review (NDA 20,406)."

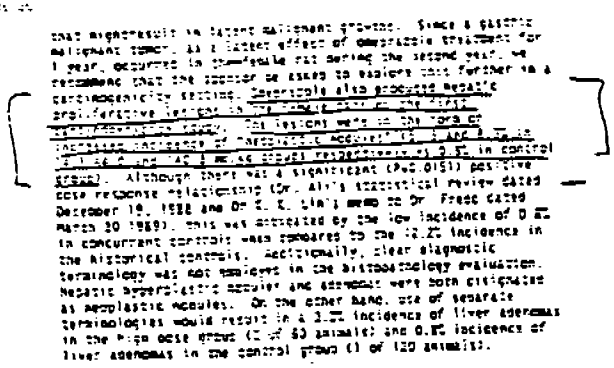
Pharmacologist's Review of NDA 19,810 (Omeprazole) provided by sponsor:

APPEARS THIS WAY ON ORIGINAL



Supervisory Pharmacologist's Addendum to Pharmacology Review of NDA 19,810 (Omeprazole) provided by sponsor:

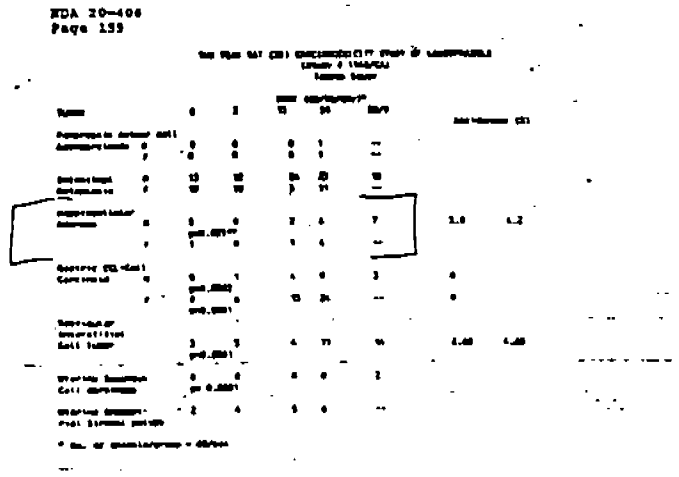
APPEARS THIS WAY ON ORIGINAL



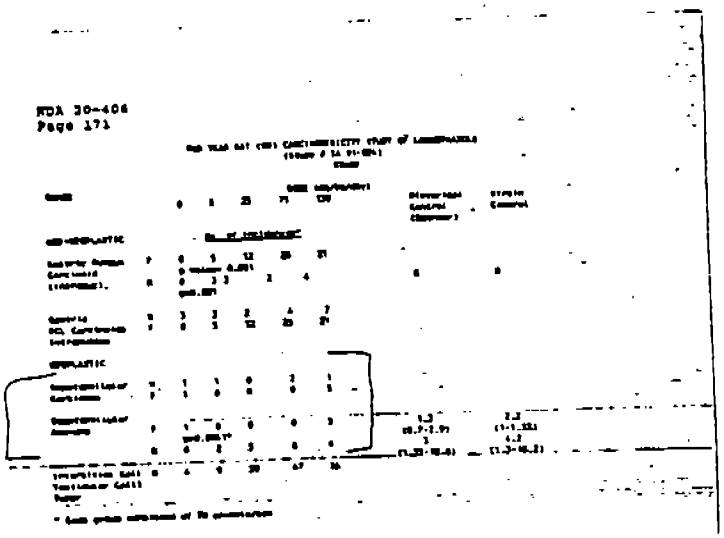
BEST POSSIBLE COPY

Pharmacologist's Review of NDA 20,406 (Lansoprazole) provided by sponsor:

APPEARS THIS WAY ON ORIGINAL



APPEARS THIS WAY ON ORIGINAL



BEST POSSIBLE COPY

Evaluation: Incidences of liver tumors for Sprague-Dawley rat carcinogenicity studies with omeprazole and lansoprazole reported by the sponsor are incorrect based upon a full review (i.e., Pharmacology Review and Supervisory Pharmacologist's Addenum to the Pharmacology Review) of each approved drug product.

The incidence rate of liver tumors in female Sprague-Dawley rats from the carcinogenicity study with omeprazole as reported by the sponsor are incorrect. If the sponsor had continued to read further in the marked paragraph from the Supervisory Pharmacologist's Addendum, they would have obtained the correct incidences. In the last sentence of the paragraph, it is stated "On the other hand, use of separate terminologies would result in a 3.3% incidence of liver adenomas in the high dose group (2 of 60 animals) and 0.8% incidence of liver adenomas in the control group (1 of 120 animals). For female rats at 138 mg/kg/day, there were 3 rats with findings of hyperplastic nodules in the liver (i.e., non-neoplastic finding) and 2 rats with findings of

hepatocellular adenomas. Thus, there was no statistically significant increase in the incidence rate of liver tumors with female Sprague Dawley rats in the carcinogenicity study with omeprazole.

The incidence rate of liver tumors in Sprague-Dawley rats from the carcinogenicity studies with lansoprazole as reported by the sponsor are incorrect. Incidence rates of liver tumors reported in the Pharmacology Review were in error; however, these incidence rates were corrected in the Supervisory Pharmacologist's Addendum as shown in the tables below. There were no statistically significant increases in the incidence rates of liver tumors with Sprague-Dawley rats in the carcinogenicity studies with lansoprazole.

Liver tumor incidence in the 2-year carcinogenicity study with lansoprazole in Sprague-Dawley rats that received oral doses of 0, 5, 15, and 50 mg/kg/day (——— Study; FATE = ALL; n = 60/group). This table was taken from the Supervisory Pharmacologist's Addendum.

Incidence* of Histopathology Lesions in Rat Carcinogenicity Study

Tissue/Organ	Sex	Dose (mg/kg/day)					
		0	0	5	15	50	50**
Liver							
Hepatocellular Adenoma:	Male	5	0	2	4	7	3
	Female	1	1	2	1	2	--
Hepatocellular Carcinoma	Male	1	0	1	1	1	0
	Female	0	0	0	0	0	--
Hepatocellular Adenoma + Carcinoma	Male	6	0	3	5	8	3
	Female	1	1	2	1	2	--
Stomach, Glandular							
Intestinal Metaplasia							
Pylorus:	Male	11	12	13	8	15	20
	Female	7	8	9	2	7	--
Fundus:	Male	0	0	0	1	2	1
	Female	0	0	0	0	1	--
Diffuse ECL Cell Hyperplasia	Male	0	0	26	27	45	31
	Female	0	0	54	63	59	--
Nodular ECL Cell Hyperplasia	Male	0	0	0	0	0	0
	Female	0	0	1	3	6	--

* Number of animals with the lesion. Total number/sex/group = 60
** Recovery group (treatment for 18 months only)

Liver tumor incidence in the 2-year carcinogenicity study with lansoprazole in Sprague-Dawley rats that received oral doses of 0, 5, 25, 75, and 150 mg/kg/day ——Study; FATE = ALL; n = 70/group). This table was taken from the Supervisory Pharmacologist's Addendum and checked against line listings from the original study in NDA 20,406.

Liver	Sex	0	5	25	75	150
Hepatocellular adenoma	M	2	0	2	1	0
	F	1	0	0	0	5
Hepatocellular carcinoma	M	1	1	0	2	1
	F	0	1	1	0	0
Hepatocellular adenoma + carcinoma	M	3	1	2	3	1
	F	1	1	1	0	5

5. ^{32}P-Postlabeling studies with hepatic DNA obtained from female Sprague-Dawley rats treated with pantoprazole at 200 mg/kg/day for 4 weeks.

Sponsor's Position: "The sponsor contends that the ^{32}P-postlabeling study did not show evidence of liver DNA adduct formation with pantoprazole compared with controls. The data are consistent with a non-genotoxic mechanism of rodent liver carcinogenesis. Based upon preliminary experiments, a final evaluation of results was performed for pantoprazole to quantify DNA adducts. The analysis used liver DNA from pantoprazole-treated animals that was prepared without a nucleotide-adduct enrichment procedure (i.e., nuclease P1 enhancement procedure was not used). The DNA digest was subjected to chromatography in an optimized system that was demonstrated to resolve tamoxifen adducts and to reveal one additional spot for nuclease P1-treated DNA from pantoprazole-treated rats. This additional spot that was observed after nuclease P1 treatment, was also observed in the nontreated DNA (i.e., no DNA-adduct enrichment procedure). The sponsor provided (1) first generation photocopies of ——— (2) tracings of the ——— and tables of counts from excised spots; and (3) transparencies of the tracings. The quantity of radioactivity present the in pantoprazole spot was not different from comparable areas from ——— of DNA from control rats."

Evaluation: The Genetic Toxicology Committee with the consultation of Drs. Beland and Kadlubar at the National Center for Toxicological Research in a memorandum dated May 21, 1999 stated as follows: "The Committee concluded that there is reasonable qualitative evidence for the formation of DNA adducts from pantoprazole. Without further information, nothing can be stated with regard to absolute levels of adducts."

——— generated in preliminary experiments suggested the presence of a distinct DNA adduct spot(s) in liver DNA obtained from pantoprazole-treated rats. This distinct adduct spot suggests that pantoprazole or one of its metabolites directly interacts with DNA. For ——— generated in preliminary experiments, samples were prepared using a nucleotide-adduct enrichment procedure (i.e., nuclease P1 enhancement) prior to ^{32}P-labeling and subsequent chromatographic separation. In the final evaluation, the sponsor quantified samples without the use of a nucleotide-

adduct enrichment procedure prior to ^{32}P-labeling. Nuclease P1 is used to cleave deoxyribonucleoside 3`-monphosphates of normal nucleotides to deoxyribonucleosides, which do not serve as substrates for ^{32}P-labeling mediated by polynucleotide kinase, while most adducted nucleotides are, in general, totally or partially resistant to the 3'-desphosphorylating action of nuclease P1 (Carcinogenesis 7: 1543-1551, 1986). Thus, use of nuclease P1 enhances sensitivity for detection of DNA adducts and in general removes normal nucleotides, which would otherwise increase the background. Further, the rate of enzymatic ^{32}P-labeling of nucleotide-adducts is, in general, slower than observed for normal nucleotides (Chem. Res. Toxicol. 12: 68-77, 1999; Carcinogenesis 9: 1687-1693, 1988; Mutagenesis 8: 121-126, 1993; Carcinogenesis 14: 2463-2469, 1993). Without the use of a nucleotide-DNA adduct enrichment procedure, such as the nuclease P1 procedure, it is conceivable that the ^{32}P-ATP labeling substrate in the assay could be depleted by the labeling of normal nucleotides prior to any labeling of nucleotide-adducts. It is also possible that labeling of nucleotide-adducts could be incomplete. The quantitation of nucleotide-adducts by the sponsor is considered to be unreliable. For further detail, see the review of Amendments submitted on May 12, 1999 and May 19, 1999 (Document Room Date of June 10, 1999) and the review of Amendments submitted on April 26, 1999 and May 11, 1999 (Document Room Date: May 21, 1999).

As noted in an earlier review of Amendments submitted on April 26, 1999 and May 11, 1999 (Document Room Date: May 21, 1999), photocopies were useless in interpretation of results. No details of individual spots were evident in photocopies as shown in hand-drawn diagrams. Further, resolution of spots was extremely poor.

6. Pantoprazole poses a genotoxic and carcinogenic risk for humans.

Sponsor's Position: The sponsor contends that pantoprazole poses no genotoxic and carcinogenic risk for humans.

Evaluation: The [redacted] concluded as follows: "There are safety concerns and the drug may not be safe for long term use in humans. The extent of risk however, is not a clear, and the risk from short-term use is probably not great. The tumor incidence information should definitely be made available if the product is approved. The relevance of the rat liver and thyroid findings for humans can be questioned based on the sponsor's proposed mechanisms. The sponsor did not, however, definitively demonstrate that these mechanisms were activated by drug treatment and responsible for the tumors observed. More problematic are the other tumor findings, the various other GI non-neuroendocrine tumors and the granulocytic leukemia if they are evaluated as real (rather than misclassifications). There is a need for evaluation of the reclassified tumor findings, given the importance of these findings in judging the apparent qualitatively different tumor response to pantoprazole. Given the genotoxicity data, the carcinogenic effect of pantoprazole may be in part dependent on genotoxic mechanisms and thus may pose a risk to humans. The positive tumor findings should be interpreted as having possible human relevance until additional data indicates otherwise."

SUMMARY AND EVALUATION:

In the Fischer 344 rat carcinogenicity study with pantoprazole, there were findings of granulocytic leukemia in the male mid and high dose groups. Granulocytic leukemia is a rare tumor for this rat strain. The sponsor contends that the low incidence of granulocytic leukemia was likely a misdiagnosis of large granular lymphocyte (LGL) leukemia, which is a common tumor finding in this rat strain. If misdiagnoses were responsible for the findings of granulocytic leukemia in the male mid and high dose treatment groups, then one might have expected these misdiagnoses to have occurred in other male rat groups, given the high prevalence of LGL leukemia. To further assess this issue, the sponsor proposes to provide the FDA with histopathology slides and paraffin blocks from the 3 animals in question, along with histopathology slides from an additional 9 male rats (i.e., 4 high-dose, 2 mid-dose, and 3 control animals) from the same study diagnosed with LGL leukemia. Providing histopathology slides as well as tissue paraffin blocks from the 3 animals in question to Dr. William Witt at the National Center for Toxicological Research for analysis, should provide some resolution as to the type of leukemia that occurred in these animals. However, the sponsor's proposal to provide histopathology slides from an additional 9 male rats from the same study diagnosed with LGL leukemia is somewhat questionable. For purposes of not introducing any potential bias into the analysis, slides from the 3 male rats diagnosed with granulocytic leukemia as well as all male rats diagnosed with LGL leukemia should be provided to Dr. Witt. Slides should be examined under blinded conditions.

Liver tumor incidences for Sprague-Dawley rat carcinogenicity studies with omeprazole and lansoprazole presented by the sponsor [redacted] were incorrect as they were based upon incomplete Pharmacology reviews. Correct liver tumor incidences for these carcinogenicity studies with omeprazole and lansoprazole based upon Pharmacology reviews in conjunction with Supervisory Pharmacologist's Addenums are presented within the present review. Neither omeprazole nor lansoprazole produced statistically significant increases in the incidences of liver tumors in Sprague-Dawley rat carcinogenicity studies with these respective compounds.

RECOMMENDATIONS:

The following information should be communicated to the sponsor.

1. With regard to the ^{32}P-Postlabeling study, the first-generation photocopies of _____ offer no additional information with regard to interpretation of study results as compared to photocopies submitted on April 26, 1999. There is no need to continue resubmitting this material. The sponsor should consider repeating the ^{32}P-postlabeling study. Each sample should be processed with and without the nuclease P1 enhancement procedure prior to ^{32}P-labeling and subsequent chromatographic separation. Background indigenous spots should be appropriately characterized. Units of quantitation should be justified.

/S/
Timothy W. Robison, Ph.D. 6-18-99
Date

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

/S/
6/18/99

R/D Init.: J. Choudary 6/16/99

TWR/hw/6/16/99 & 6/18/99

APPEARS THIS WAY
ON ORIGINAL

Walsh

NDA 20,987

PHARMACOLOGIST'S REVIEW OF NDA 20,987
(Amendment Dated January 28, 1999)

Sponsor & Address: Wyeth Ayerst Research
P.O. Box 8299
Philadelphia, PA 19101-82

JUN 10 1999

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

Date of Submission: January 28, 1999

Date of HFD-180 Receipt: January 29, 1999

Date of Review: June 9, 1999

Drug: Pantoprazole (PROTONIX™)

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

Submission Contents:

Correspondence from the sponsor regarding Histopathological Reanalysis of Tumors from selected Sprague-Dawley rats of the Carcinogenicity Study with Pantoprazole (Appendix 7).

[redacted] submitted an application on September 13, 1991 to the Agency to allow the initiation of development of pantoprazole as a treatment for gastroesophageal reflux disease (GERD) in the United States (see IND [redacted] [redacted] conducted a two-year carcinogenicity study with pantoprazole in Sprague Dawley rats. The study was initiated on October 3, 1989, the last date of necropsy was on October 10, 1991, and the report was issued on January 13, 1993. The study director was [redacted] MRCVS, MMedVet. Authors of the report were [redacted] MRCVS, MMedVet, Study Director and Study Pathologist, and [redacted] BS, Associate Scientist, Drug Analysis. The study received management approval from [redacted] D.V.M. M.Sc., Group Director, Toxicology-U.S., and [redacted] Ph.D., Director, Morphologic Pathology and Histotechnology. Macroscopic and microscopic reports for each animal were signed by Study Director, [redacted], MRCVS, MMedVet.

Evaluation: None.

2. Animal number 5100 (200 mg/kg/day, female).

Original Report from [redacted] The original study report listed separate findings of a malignant chief cell adenocarcinoma in the fundus with vascular invasion and multiple malignant neuroendocrine (NE) cell tumors in the fundus with submucosal and vascular invasion.

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "The tissue was comprised of a large mass of neoplastic tissue within the gastric wall. The neoplastic tissue of the identified tumors was contiguous but had widely varying morphologic features. In one region, there were neoplastic cells with features consistent with a classical NE-cell tumor. In another region, the cells grew in a cuboidal to columnar epitheloid pattern, frequently forming pseudoglandular structures and often with abundant and deeply eosinophilic cytoplasm. These regions had an appearance consistent with an adenocarcinoma of chief cells derived from the glandular gastric epithelium. Based upon these features, the original diagnoses of both NE cell-tumor and chief-cell adenocarcinoma (merging or collision) were considered reasonable, although debatable, diagnoses. Other alternative diagnoses were NE-cell tumor with morphologic features of chief-cell differentiation or chief-cell adenocarcinoma with features of NE-cell differentiation. Based on these uncertainties, Dr. Germann was asked to perform histochemical (Grimelius silver) and immunohistochemical (neuron-specific enolase [NSE] and chromogranin) stains to attempt a definitive identification of the cell type(s) within the tumor. At a later date, Dr. Germann informed the reviewing pathologists that a small percentage of the cells stained positively with Grimelius silver stain and chromogranin. In addition, a large percentage of the cells stained positively with NSE. The final consensus of the reviewing pathologists was that this was a NE-cell tumor with areas of chief-cell-like differentiation."

Evaluation: The original findings in fundus consisted of a malignant chief cell adenocarcinoma and multiple malignant neuroendocrine (NE) cell tumors. The sponsor's reanalysis has reclassified the chief cell adenocarcinoma as a NE-cell tumor with areas of chief-cell-like differentiation. The original diagnosis and the reanalysis appear to agree that there was a merging or collision of NE-cells and chief-cells. The original tumor diagnosis appears unchanged; although, different terminology is used to describe the finding. It is not clear whether the staining procedures performed by Dr. Germann were done with freshly cut sections or previously stained slides, as this animal was not mentioned in GTR-31279. Analysis of this tumor by an independent group of pathologists is needed to confirm the diagnoses of this tumor.

3. Animal number 4908 (50 mg/kg/day, male).

Original Report from [redacted] The original study report listed a malignant adenocarcinoma in the pyloric region at the gastroduodenal junction.

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "The reviewing pathologists agreed with the diagnosis of adenocarcinoma. However, it was evident in the section that the tumor originated from Brunner's glands in the duodenum with infiltration below the pyloric mucosa. Therefore, this tumor was a primary tumor of duodenum rather than stomach and represented an adenocarcinoma of Brunner's glands."

Evaluation: Reanalysis has confirmed an adenocarcinoma; although, the original report listed the location of the tumor in the pyloric region at the gastroduodenal junction, while reanalysis suggested that the tumor originated from Brunner's glands in the duodenum with infiltration below the pyloric mucosa. In the original report from [redacted] the only neoplastic finding listed for the small intestine was a malignant histiocytic sarcoma in the duodenum. The validity of the reanalysis is somewhat questionable.

STOMACH AND LYMPH NODE

1. Animal number 5108 (200 mg/kg/day, female).

Original Report from [redacted] The original study report listed NE-cell tumors in the stomach with metastases in lung, liver, duodenum, mesenteric lymph node, and pancreas.

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "Additional special stains and immunohistochemistry by Byk Gulden showed that the primary stomach tumor and the various metastatic tumors stained positive with Grimelius silver stain and with chromogranin which confirmed the diagnoses of NE-cell tumors (GTR-31279). The reviewing pathologists agreed with the diagnoses made by the study pathologist. More recently, this gastric tumor was stained with NSE and synaphthophysin which also confirmed the diagnosis of malignant NE-cell tumor of stomach."

Evaluation: None.

2. Animal number 4870 (50 mg/kg/day, male).

Original Report from [redacted] The original study report listed under LYMPH NODE(S): a malignant neuroendocrine cell tumor, metastatic site, lymph node, - Lesion 1 (Firm, nodular mass adjacent to pancreas). Findings in the fundus included a malignant neuroendocrine cell tumor that was classified as metastasizing. No abnormalities were detected in the pancreas.

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "Additional special stains and immunohistochemistry by Byk Gulden showed that the tumors reacted negatively with chromogranin (stomach tumor) and Grimelius silver stain (stomach and lymph node tumors) indicating that these tumors were not NE-cell tumors (GTR-31279). In addition, these tumors stained strongly positive for lipase indicating that the tumors were acinar-cell carcinomas from the pancreas (GTR-31279). The reviewing pathologists examined the sections of stomach and lymph node, evaluated the results of special staining, and agreed with the diagnosis of acinar-cell carcinoma of the pancreas."

Evaluation: Malignant neuroendocrine cell tumors in the stomach and lymph node(s) adjacent to the pancreas listed in the original report were reclassified as acinar-cell carcinomas of the pancreas after reanalysis. The original study report listed no abnormalities for the pancreas. It is difficult to understand how these neuroendocrine cell tumors were reclassified as acinar-cell carcinomas of the pancreas in the apparent absence of a primary acinar-cell carcinoma in the pancreas. Analysis of the pancreas and tumors in the stomach and lymph node(s) adjacent to pancreas by an independent group of pathologists is needed to confirm these diagnoses.

3. Animal number 5070 (200 mg/kg/day, female).

Original Report from [redacted] The original study report listed findings of a malignant neuroendocrine cell tumor in a lymph node near the pancreas (metastatic site) and multiple, malignant neuroendocrine cell tumors in the fundus that were metastasizing with submucosal and vascular invasion.

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "Additional special stains and immunohistochemistry showed that the tumors in the stomach and lymph node were negative for NE activity (Grimelius silver stain and chromogranin) (GTR-31279). The tumors did not stain positively with any immunohistochemical stains applied (insulin, gastrin, or lipase) for pancreatic activity but were diagnosed as carcinomas of unknown origin with morphology similar to a pancreatic acinar-cell tumor (GTR-31279). The reviewing pathologists examined the sections of stomach and lymph node and agreed with the diagnosis of acinar-cell carcinoma of the pancreas."

Evaluation: A malignant neuroendocrine cell tumor in a lymph node near the pancreas and multiple, malignant neuroendocrine cell tumors in the fundus in the original report

were reclassified as acinar-cell carcinomas of the pancreas following reanalysis. Use of special stains and immunohistochemistry with tumors in the lymph node near the pancreas and fundus were inconclusive for either tumor type. Reanalysis made no definitive identification of these tumors. Analysis tumors in the stomach and lymph node adjacent to pancreas by an independent group of pathologists is needed to confirm these diagnoses.

LIVER

1. Animal Numbers 4718 (5 mg/kg/day, male) and 4997 (200 mg/kg/day, male).

Original Report from [redacted] The original study report for both animals listed a finding of a malignant NE-cell tumor in the liver (site of origin not determined). No abnormalities were listed in the pancreas for either animal.

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "These tumors were subsequently diagnosed as metastatic islet-cell carcinomas from pancreas based upon the morphologic appearance and strong positive immunostaining for insulin (GTR-31279). The reviewing pathologists agreed with this diagnosis."

Evaluation: The original study report listed no abnormalities for the pancreas for either animal. It is difficult to understand how these neuroendocrine cell tumors were reclassified as metastatic islet-cell carcinomas from pancreas in the apparent absence of a primary islet-cell carcinoma in the pancreas. With Grimelius silver stain, target cells from animal number 4718 displayed a slight positive reaction, while target cells from animal number 4997 displayed a slight to strong positive reaction. These staining reactions are consistent with the original diagnoses of neuroendocrine cell tumors. For both animals, analysis of the pancreas and tumors in the liver by an independent group of pathologists is needed to confirm these diagnoses.

2. Animal number 4883 (50 mg/kg/day, male).

Original Report from [redacted] The original study report listed a finding of a malignant NE-cell tumor in the liver (site of origin not determined).

Histopathological Review by Wyeth Ayerst Research and Byk Gulden: "The tumor did not stain with Grimelius silver stain or chromogranin suggesting that it was not a NE-cell tumor; it also did not stain for insulin or glucagon, suggesting that it was not a metastatic pancreatic tumor (GTR-31279). The cytological appearance of the cells, the growth pattern, and positive staining for actin and S 100 indicate that the tumor is likely to be an anaplastic sarcoma (GTR-31279). The reviewing pathologists agreed that anaplastic sarcoma was the most appropriate diagnosis."

Evaluation: Anaplastic sarcomas in rat liver appears to be rare (In: Pathobiology of Tumors in Laboratory Animals. Editor: V.S. Turusov. International Agency for Research

on Cancer Animals. Lyon. 1987, Part 2, Pages 48-50). Analysis of the tumor in the liver by an independent group of pathologists is needed to confirm this diagnosis.

SUMMARY AND EVALUATION

Pantoprazole is an inhibitor of gastric parietal cell H^+,K^+-ATPase under development for treatment of GERD. In support of the development of this agent, a carcinogenicity study with pantoprazole in Sprague Dawley rats was conducted by [redacted] Pantoprazole doses in the 104-week carcinogenicity study were 0.5, 5, 50, and 200 mg/kg/day. Subsequent sponsors, Wyeth Ayerst Research and Byk Gulden, conducted a histopathological reanalysis of several tumors, which were determined to be rare or unusual. It should be noted that the majority of individuals who participated in this reanalysis of tumors were representatives of the sponsors, Wyeth Ayerst Research and Byk Gulden.

Animal numbers 5001 (200 mg/kg/day, male), 5055 (200 mg/kg/day, male), and 5122 (200 mg/kg/day, female) were identified with findings of typical adenomatous polyps in the glandular stomach in the original report. There were no changes following reanalysis.

Animal number 5100 (200 mg/kg/day, female) was identified with separate findings in the fundus of a malignant chief cell adenocarcinoma and multiple malignant neuroendocrine (NE) cell tumors in the original report. Reanalysis led to a reclassification of the chief cell adenocarcinoma as a NE-cell tumor with areas of chief-cell-like differentiation. The original diagnosis and the reanalysis appear to agree that there was a merging or collision of NE-cells and chief-cells. The original tumor diagnosis appears unchanged; although, different terminology is used to describe the finding.

Animal number 4908 (50 mg/kg/day, male) was identified with a malignant adenocarcinoma in the pyloric region at the gastroduodenal junction in the original report. Reanalysis suggested that this tumor was a primary tumor of duodenum rather than stomach and represented an adenocarcinoma of Brunner's glands. In the original report from [redacted] the only neoplastic finding listed for the small intestine was a malignant histiocytic sarcoma in the duodenum. The validity of the reanalysis is somewhat questionable.

Animal number 5108 (200 mg/kg/day, female) was identified with NE-cell tumors in the stomach with metastases in lung, liver, duodenum, mesenteric lymph node, and pancreas. There were no changes following reanalysis.

Animal number 4870 (50 mg/kg/day, male) was identified with a malignant neuroendocrine cell tumor (metastatic site) in a lymph node adjacent to the pancreas) and a malignant neuroendocrine cell tumor in the fundus (metastasizing). Both tumors were reclassified as acinar-cell carcinomas of the pancreas after reanalysis. The

original study report listed no abnormalities for the pancreas. It is difficult to understand how these neuroendocrine cell tumors were reclassified as acinar-cell carcinomas of the pancreas in the apparent absence of a primary acinar-cell carcinoma in the pancreas.

Animal number 5070 (200 mg/kg/day, female) was identified with a malignant neuroendocrine cell tumor in a lymph node near the pancreas (metastatic site) and multiple, malignant neuroendocrine cell tumors in the fundus (metastasizing) in the original report. Both tumors were reclassified as acinar-cell carcinomas of the pancreas following reanalysis. However, use of special stains and immunohistochemistry were inconclusive with regard to identification of the neoplastic findings as either neuroendocrine cell tumors or acinar-cell carcinomas. Reanalysis made no definitive identification of these tumors.

Animal numbers 4718 (5 mg/kg/day, male) and 4997 (200 mg/kg/day, male) were both reported with a finding of a malignant NE-cell tumor in the liver (site of origin not determined) in the original report. These tumors were subsequently diagnosed as metastatic islet-cell carcinomas following reanalysis. The original study report listed no abnormalities for the pancreas for either animal. It is difficult to understand how these neuroendocrine cell tumors were reclassified as metastatic islet-cell carcinomas from pancreas in the apparent absence of a primary islet-cell carcinoma in the pancreas.

Animal number 4883 (50 mg/kg/day, male) was reported listed a finding of a malignant NE-cell tumor in the liver (site of origin not determined). The tumor was reclassified as an anaplastic sarcoma following reanalysis. Anaplastic sarcomas in rat liver appears to be rare (In: Pathobiology of Tumors in Laboratory Animals. Editor: V.S. Turusov. International Agency for Research on Cancer Animals. Lyon. 1987, Part 2, Pages 48-50).

The group of pathologists, who participated in the histopathological reanalysis of several tumors, from the Sprague-Dawley rat carcinogenicity study with pantoprazole, appears to have been inappropriate as these individuals were representatives of successive sponsors, Byk Gulden and Wyeth Ayerst Research. Independent analysis of these tumors should be performed by a group of pathologists with no potential conflicts of interests to the Pharmaceutical Industry and in particular, [redacted] Byk Gulden, and Wyeth Ayerst Research.

Recommendations: With regard to the carcinogenicity study with pantoprazole in Sprague Dawley rats, the sponsor should provide answers to questions listed below. Further, organ and tissue histopathology slides as listed below, should be provided for independent analysis by a group of pathologists with no potential conflicts of interests to the Pharmaceutical Industry and in particular, [redacted] Byk Gulden, and Wyeth Ayerst Research.