

MEMORANDUM

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

DATE: October 29, 1999

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

SUBJECT: NDA 20,987 (PROTONIX/Pantoprazole Sodium
Delayed-Release Tablets) -
Amendment Dated July 30, 1999 -
Sponsor's Revised Draft Labeling.

TO: NDA 20,987

In the approvable letter dated June 30, 1999, the sponsor was provided labeling and asked to submit the final printed labeling identical in content to the supplied marked-up copy. Sponsor in their response dated July 30, 1999, submitted a revised draft labeling with several changes. The changes in the preclinical portions of the labeling are reviewed below. They are arranged in the following order: FDA draft, Wyeth-Ayerst's revised draft, evaluation, recommendation and FDA final draft. The page numbers refer to the numbers of Wyeth-Ayerst's revised draft labeling and the circled paragraph numbers are also the numbers used by Wyeth-Ayerst in their revised draft labeling.

10 PAGE(S) REDACTED

Draft

Labeling

DW
WALSH

MEMORANDUM

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

DATE: October 6, 1999

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

SUBJECT: NDA 20,987 Amendment dated October 1, 1999 containing a Draft Report for a 28-Day Repeated Dose Oral Toxicity Study in Mice and a Protocol for a Twenty-six Week Oral Gavage Carcinogenicity Study in Male and Female p53 (+/-) Mice - Needed Information.

TO: NDA 20,987

The amendment submitted by Wyeth-Ayerst Research on October 1, 1999 containing a dose range finding study in mice (Sponsor Study #98103) to be used for selection of doses in the p53(+/-) transgenic mouse carcinogenicity study provides no histopathology findings for female treatment groups. The amendment states that a draft report containing histopathologic evaluation of tissues from female mice is anticipated on October 4, 1999. A complete analysis and review of the dose range finding study in mice cannot be performed until histopathology findings for all female treatment groups have been provided by the sponsor.

It would also be helpful in the analysis and review of this dose range finding study in mice, if any available gross pathological or histopathological findings for animals that died during the treatment period could be provided.

Therefore, the sponsor should be asked to provide the following information in an expeditious manner: (a) histopathologic evaluation of tissues from female mice in the 28-day dose range finding study (Sponsor Study #98103), and (b) any available gross pathological or histopathological findings for animals that died during the treatment period of the 28-day dose range finding study (Sponsor Study #98103).

/S/

Timothy W. Robison, Ph.D.

10-6-99

Date

/S/

10/6/99

W ALSK

MEMORANDUM

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

DATE: October 8, 1999

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

SUBJECT: NDA 20,987 Amendment dated October 1, 1999 containing a Draft Report for a 28-Day Repeated Dose Oral Toxicity Study in Mice and a Protocol for a Twenty-six Week Oral Gavage Carcinogenicity Study in Male and Female p53 (+/-) Mice - Needed Information.

TO: NDA 20,987

The amendment submitted by Wyeth-Ayerst Research on October 1, 1999 containing a dose range finding study in mice (Sponsor Study #98103) did not identify the sources of lansoprazole and omeprazole used in the study. Were these drugs manufactured by the sponsor or were they purchased from a supplier? How do these drugs compare to those in clinical use? For this dose range finding study in mice, histopathology slides were apparently evaluated by two pathologists. One pathologist appears to be a representative of the contract laboratory, while the other pathologist is a representative of Wyeth-Ayerst Research Drug Safety. An apparent agreement by the two pathologists will be achieved on the final results of all lesions. In the review of this study, it would be helpful to have the individual findings of each pathologist as well as the consensus results.

Therefore, the sponsor should be asked to provide the following information in an expeditious manner: (a) the sources of omeprazole and lansoprazole used in the study (Sponsor Study #98103) and how they compare to the drugs in clinical use, and (b) findings of each pathologist for analysis of study tissues and the consensus results obtained from the two pathologists.

TSI

Timothy W. Robison, Ph.D.

10-8-99

Date

TSI

10/8/99

**Atlas
of
Tumor Pathology**

**Tumors
of the
Esophagus and Stomach**

by
**Klaus J. Lewin, M.D., FRCPath and
Henry D. Appelman, M.D.**



AFIP

Tumors of the Esophagus and Stomach

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Small Cell (Oat Cell) Carcinoma

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Mixed Endocrine and Nonendocrine Epithelial Tumors

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MEMORANDUM

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

LW/SK

Date: June 10, 1999

To: Dr. William Witt, National Center for Toxicological Research

Subject: NDA 20-987 (Protonix Tablets) – Carcinogenicity Studies

From: Jasti Choudary, Ph.D., B.V.Sc., Pharmacology Team Leader
 Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
 Office of Drug Evaluation III, Center for Drug Evaluation and Research

As per Dr. DeGeorge's conversation with you, the following particulars are provided to facilitate your independent histopathology evaluation of the materials sent to you. The sponsor (Wyeth-Ayerst) has been asked to provide the following materials the details of which are listed. The sponsor intends to include additional control and spontaneous tumor material for blinded comparison. The distinction between the sponsor's original calls for these various tumors and the revised calls in conjunction with other information, such as genotoxicity findings, is important in our deliberations on the strength and qualitative difference of the carcinogenic signal between this and related pharmaceuticals.

Fischer Rat Carcinogenicity Study

| <u>Animal #</u> | <u>Dose Mg/kg/Day</u> | <u>Original Finding Byk-Gulden</u> | <u>Present (Wyeth-Ayerst) Sponsor's Changed Diagnosis</u> | <u>Materials to be Provided</u> |
|-----------------|---------------------------|--|---|---|
| 83 (Male) | 15 | Granulocytic Leukemia | Claims to be mononuclear cell leukemia/large granular lymphocyte leukemia | Slide and Paraffin Block |
| 41 (Male) | 50 | " | " | " |
| 410 (Male) | 50 | " | " | " |

Sprague – Dawley Rat Carcinogenicity Study

| <u>Animal #</u> | <u>Dose Mg/kg/Day</u> | <u>Original Finding</u> | <u>Present (Wyeth-Ayerst) Sponsor's Changed Diagnosis</u> | <u>Materials to be Provided</u> |
|------------------|---------------------------|--|---|--|
| 5100 (Female) | 200 | Stomach: Fundus 1-Chief cell adenocarcinoma 2-Multiple neuroendocrine cell tumors | "Debatable" – Neuroendocrine cell tumors with areas of chief cell-like differentiation, or Chief cell adenocarcinoma with features of neuroendocrine cell differentiation. | 1-Original Slides from — 2-Subsequent slides prepared by Wyeth- Ayerst 3-Original paraffin block |

CSO/1003/99

MEMORANDUM

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

DATE: April 26, 1999

APR 29 1999

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

SUBJECT: NDA 20,987 (PROTONIX™/Pantoprazole
Sodium Tablets) - Labeling -
Preclinical Portions.

TO: NDA 20,987

This is a follow-up to Dr. Robison's Pharmacology Review of NDA 20,987 dated April 20, 1999. The following represents the recommended version of portions of the sponsor's proposed labeling which are based on preclinical pharmacology and toxicology data. The corresponding portions in the sponsor's version should be deleted and replaced by the present Pharmacology version.

1. "CLINICAL PHARMACOLOGY"

Pharmacodynamics

Enterochromaffin-Like (ECL) Cell Effects

2. "PRECAUTIONS"

a. Carcinogenesis, Mutagenesis, Impairment of Fertility

b. Pregnancy. Teratogenic Effects. Pregnancy Category.

c. Nonteratogenic Effects

3. "OVERDOSAGE"

2 PAGE(S) REDACTED

DRAFT

Labeling

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Jasti B. Choudary, B.V.Sc., Ph.D.

cc:

NDA 20,987

HFD-180

HFD-181/CSO, Ms. Walsh

HFD-180/Dr. Choudary

HFD-180/Dr. Robison

JBC/hw/4/29/99

CSO/Walsh

MEMORANDUM

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

DATE: April 12, 1999

APR 12 1999

FROM: Timothy W. Robison, Ph.D.
Pharmacologist

SUBJECT: NDA 20,987 - Study entitled " Pantoprazole: Studies on the Hepatic Effects of Pantoprazole, Lansoprazole, and Omeprazole in Rats (GTR-32977)" in Volume 1.077.

TO: NDA 20,987

The description of methodology and presentation of results with regard to ³²P-Postlabeling Studies in GTR-32977 of Volume 1.077 is incomplete. Quantitation of DNA adducts/10⁸ nucleotides in Table 1 on page 36 (see Table 1 below) does not appear to correlate with ³²P-Postlabeling Results described in Appendix 3 beginning on page 56. Page numbers referenced are those in lower right hand corner. Data described for pantoprazole in Appendix 3 following nuclease P1 in chromatography systems 1, 3, and 4 were taken to construct Table 2 (See below). Data in Tables 1 and 2 do not correlate with one another. Further, the presentation of data in Appendix 3 is incomplete as quantities for all individual adducts have not been provided to allow a summation to obtain a total.

It should be communicated to the sponsor that the description of methodology and presentation of results with regard to ³²P-Postlabeling Studies in GTR-32977 is incomplete. The sponsor should be asked to provide a detailed description of methodology. With regard to results, copies of all _____ produced in each experiment should be provided. All adducts in each sample should be identified. Adducts should be identified on each _____ in such a manner, so that it is possible to correlate each adduct spot with its quantity in a separate table. Further, it should be made possible to add the quantities of individual adducts for each sample to obtain the total number of adducts for each sample. With either butanol extraction or Nuclease P1 enhancement, results for each _____ system should be provided separately. Results with tamoxifen, lansoprazole, omeprazole, and pantoprazole should be provided separately.

Table 1. Number of adducts/10⁸ nucleotides detected in the Omeprazole and Pantoprazole spots and background values for the equivalent areas in controls

| | | Exp. 1 | Exp. 2 | Exp. 3 | Mean | SD | Average | SD | Significance |
|-------------------------|-------------------------|--------|--------|--------|-------|------|---------|------|--------------|
| Omeprazole | 200mg/kg | 1 | _____ | _____ | 2.28 | 1.5 | 2.30 | 0.2 | NS |
| | | 2 | _____ | _____ | 2.11 | 0.6 | | | |
| | | 3 | _____ | _____ | 2.5 | 0.9 | | | |
| | 600mg/kg | 1 | _____ | _____ | 2.82 | 0.6 | 2.52 | 0.5 | NS |
| | | 2 | _____ | _____ | 2.81 | 0.5 | | | |
| | | 3 | _____ | _____ | 1.93 | 0.8 | | | |
| Control (Background) | 1 | _____ | _____ | 2.13 | 1.8 | 1.90 | 0.5 | | |
| | 2 | _____ | _____ | 2.18 | 2.3 | | | | |
| | 3 | _____ | _____ | 1.29 | 0.9 | | | | |
| Pantoprazole | 200mg/kg | 1 | _____ | _____ | 8.04 | 5.8 | 10.26 | 1.96 | NS |
| | | 2 | _____ | _____ | 11.74 | 6.0 | | | |
| | | 3 | _____ | _____ | 11 | 3.7 | | | |
| | Control (Background) | 1 | _____ | _____ | 7.22 | 4.2 | 7.53 | 1.5 | |
| | | 2 | _____ | _____ | 9.11 | 5.8 | | | |
| | | 3 | _____ | _____ | 6.27 | 3.2 | | | |

* No visible spot

NS, no significant difference between the dosed and the corresponding control (background) samples.

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Table 2. Number of DNA adducts/10⁸ nucleotides in Control and Pantoprazole treated samples in chromatography systems 1, 3, and 4 following nuclease P1 enhancement.

| Solvent System 1 | | | |
|-------------------|--------------|-------------|--------------|
| Experiment Number | Spot | Control | Pantoprazole |
| 5 | Common | 14.8 | 8.5 |
| | Extra | | 11 |
| 6 | Common | 48 | 10 |
| | Extra-1 | | 12.6 |
| | Extra-2 | | 6.3 |
| 8 | Common | 14 | 12 |
| | Extra-1 | | 19.9 |
| | Total | 42.2 | 73.6 |
| Solvent System 3 | | | |
| Experiment Number | Spot | Control | Pantoprazole |
| 5 | Common | 9.6 | 9.6 |
| | Extra | | 9.1 |
| | Total | 85.8 | 84.1 |
| 8 | Common | 9.3 | 9.3 |
| | Extra | | 17.3 |
| | Total | 57.3 | 113.9 |
| Solvent System 4 | | | |
| Experiment Number | Spot | Control | Pantoprazole |
| 5 | Common | 15.5 | 15.5 |
| | Extra | | 22.3 |
| | Total | 37.8 | 87.8 |
| 8 | Common | 11.3 | 11.3 |
| | Extra | | 19.5 |
| | Total | 38.8 | 89.4 |

/S/

Timothy W. Robison, Ph.D.

4-12-99
Date

cc:
Orig. NDA 20,987
HFD-180
HFD-181/CSO/ Ms. Walsh
HFD-180/Dr. Choudary
HFD-180/Dr. Robison
HFD-180/Dr. Talarico
HFD-180/Dr. Gallo-Torres

/S/ 4/12/99

R/D Init.: J. Choudary 4/12/99

TWR/hw/4/12/99

DATE: September 24, 1998
 TO: Maria Walsh
 FROM: Tim Robison, Ph.D.
 RE: NDA 20,987 (Pantoprazole)

For the following study reports entitled Study for Assessing the Tumor Promoting Activity of Pantoprazole in Stomach and Forestomach in Sprague Dawley Rats (GTR-33036) and Study for Assessing the Tumor Promoting Activity of Pantoprazole in Liver and Thyroid in Sprague Dawley Rats (GTR-33037), 24 rats/sex/group were used. However, complete gross pathological and histopathological examinations were only performed for 20 rats/sex/group in both studies. Gross pathological and histopathological examinations should be provided for all animals in these studies. I have provided lists of animals in the two studies that were not subjected to gross pathological and histopathological examinations. Could you please ask the sponsor for this data. Thank you.

Study for Assessing the Tumor Promoting Activity of Pantoprazole in Stomach and Forestomach in Sprague Dawley Rats (GTR-33036).

The following animals (4 rats/sex/group) were not subjected to gross pathological or histopathological examinations.

| Group | Sex/Animal number | Day of Death | Cause of death |
|---------------------|-------------------|--------------|--------------------|
| Control | Male, #010008 | End of Study | Terminal sacrifice |
| Control | Male, #010022 | End of Study | Terminal sacrifice |
| Control | Male, #010023 | End of Study | Terminal sacrifice |
| Control | Male, #010024 | End of Study | Terminal sacrifice |
| Control | Female, #020021 | End of Study | Terminal sacrifice |
| Control | Female, #020022 | End of Study | Terminal sacrifice |
| Control | Female, #020023 | End of Study | Terminal sacrifice |
| Control | Female, #020024 | End of Study | Terminal sacrifice |
| MNNG + Pantoprazole | Male, #030001 | Day 55 | Accidental death |
| MNNG + Pantoprazole | Male, #030003 | Day 119 | Moribund sacrifice |
| MNNG + Pantoprazole | Male, #030006 | Day 80 | Moribund Sacrifice |
| MNNG + Pantoprazole | Male, #030014 | Day 92 | Died |
| MNNG + Pantoprazole | Female, #040003 | Day 76 | Moribund Sacrifice |
| MNNG + Pantoprazole | Female, #040007 | Day 67 | Accidental death |
| MNNG + Pantoprazole | Female, #040008 | Day 46 | Accidental death |
| MNNG + Pantoprazole | Female, #040013 | Day 77 | Died |
| MNNG + Vehicle | Male, #050006 | Day 122 | Moribund Sacrifice |
| MNNG + Vehicle | Male, #050008 | Day 41 | Accidental death |
| MNNG + Vehicle | Male, #050009 | Day 205 | Died |
| MNNG + Vehicle | Male, #050024 | Day 85 | Moribund Sacrifice |
| MNNG + Vehicle | Female, #060002 | Day 72 | Died |
| MNNG + Vehicle | Female, #060004 | Day 57 | Died |
| MNNG + Vehicle | Female, #060015 | Day 105 | Moribund Sacrifice |
| MNNG + Vehicle | Female, #060021 | Day 49 | Died |

| | | | |
|--------------|-----------------|--------------|--------------------|
| Pantoprazole | Male, #070003 | Day 267 | Moribund Sacrifice |
| Pantoprazole | Male, #070022 | End of Study | Terminal sacrifice |
| Pantoprazole | Male, #070023 | End of Study | Terminal sacrifice |
| Pantoprazole | Male, #070024 | End of Study | Terminal sacrifice |
| Pantoprazole | Female, #080008 | End of Study | Terminal sacrifice |
| Pantoprazole | Female, #080018 | End of Study | Terminal sacrifice |
| Pantoprazole | Female, #080021 | End of Study | Terminal sacrifice |
| Pantoprazole | Female, #080024 | End of Study | Terminal sacrifice |

Study for Assessing the Tumor Promoting Activity of Pantoprazole in Liver and Thyroid in Sprague Dawley Rats (GTR-33037).

The following animals (4 rats/sex/group) were not subjected to gross pathological or histopathological examinations.

| Group | Sex/Animal number | Day of Death | Cause of death |
|-----------------------|-------------------|--------------|---------------------|
| Control | M #010001 | 218 | Moribund sacrifice |
| Control | M #010010 | 155 | Moribund sacrifice |
| Control | M #010018 | 285 | Died |
| Control | M #010024 | End of Study | Terminal Sacrifice |
| Control | F #020004 | 381 | Moribund sacrifice |
| Control | F #020022 | End of Study | Terminal Sacrifice |
| Control | F #020023 | End of Study | Terminal Sacrifice |
| Control | F #020024 | End of Study | Terminal Sacrifice |
| NMU + Pantoprazole | M #030002 | 39 | Gavage error |
| NMU + Pantoprazole | M #030003 | 39 | Gavage error |
| NMU + Pantoprazole | M #030019 | 158 | Gavage error |
| NMU + Pantoprazole | M #030022 | 48 | Gavage error |
| NMU + Pantoprazole | F #040001 | 39 | Gavage error |
| NMU + Pantoprazole | F #040003 | 39 | Gavage error |
| NMU + Pantoprazole | F #040004 | 39 | Gavage error |
| NMU + Pantoprazole | F #040005 | 39 | Gavage error |
| NMU + Veh. Of Pantop. | M #050004 | 400 | Moribund Sacrifice |
| NMU + Veh. Of Pantop. | M #050005 | End of Study | Terminal Sacrifice. |
| NMU + Veh. Of Pantop. | M #050017 | 52 | Died (Replaced) |
| NMU + Veh. Of Pantop. | M #050020 | 385 | Died |
| NMU + Veh. Of Pantop. | F #060001 | 126 | Died |
| NMU + Veh. Of Pantop. | F #060003 | 228 | Moribund Sacrifice |
| NMU + Veh. Of Pantop. | F #060007 | 288 | Moribund Sacrifice |
| NMU + Veh. Of Pantop. | F #060008 | 253 | Moribund Sacrifice |
| Veh. of NMU + Pantop. | M #070001 | 191 | Gavage error |
| Veh. of NMU + Pantop. | M #070012 | 284 | Died |
| Veh. of NMU + Pantop. | M #070015 | 80 | Gavage error |
| Veh. of NMU + Pantop. | M #070019 | 164 | Died |
| Veh. of NMU + Pantop. | F #080003 | 39 | Gavage error |
| Veh. of NMU + Pantop. | F #080004 | 39 | Gavage error |
| Veh. of NMU + Pantop. | F #080011 | 59 | Gavage error |
| Veh. of NMU + Pantop. | F #080016 | 77 | Died |
| NMU + Phenobarbital | M #90014 | 318 | Moribund Sacrifice |
| NMU + Phenobarbital | M #90022 | End of Study | Terminal Sacrifice |
| NMU + Phenobarbital | M #90023 | End of Study | Terminal Sacrifice |
| NMU + Phenobarbital | M #90024 | End of Study | Terminal Sacrifice |
| NMU + Phenobarbital | F #100001 | 388 | Moribund Sacrifice |
| NMU + Phenobarbital | F #100008 | 231 | Died |

| | | | |
|---------------------|-----------|--------------|----------------------------------|
| NMU + Phenobarbital | F #100022 | 373 | Moribund Sacrifice |
| NMU + Phenobarbital | F #100024 | End of Study | Terminal Sacrifice |
| NMU + Veh. of PB | M #110001 | 388 | Moribund Sacrifice |
| NMU + Veh. of PB | M #110022 | End of Study | Terminal Sacrifice |
| NMU + Veh. of PB | M #110023 | End of Study | Terminal Sacrifice |
| NMU + Veh. of PB | M #110024 | End of Study | Terminal Sacrifice |
| NMU + Veh. of PB | F #120011 | 352 | Moribund Sacrifice |
| NMU + Veh. of PB | F #120016 | 290 | Moribund Sacrifice |
| NMU + Veh. of PB | F #120018 | 290 | Moribund Sacrifice |
| NMU + Veh. of PB | F #120021 | 164 | Moribund Sacrifice |
| Veh. of NMU + PB | M #130004 | End of Study | Terminal Sacrifice (Replaced) |
| Veh. of NMU + PB | M #130010 | 368 | |
| Veh. of NMU + PB | M #130023 | End of Study | Terminal Sacrifice |
| Veh. of NMU + PB | M #130024 | End of Study | Terminal Sacrifice |
| Veh. of NMU + PB | F #140017 | 358 | Moribund Sacrifice |
| Veh. of NMU + PB | F #140022 | 205 | Moribund Sacrifice |
| Veh. of NMU + PB | F #140023 | End of Study | Terminal Sacrifice |
| Veh. of NMU + PB | F #140024 | End of Study | Terminal Sacrifice |

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