MEMORANDUM OF TELECON

DATE: January 24, 2000

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole sodium) Delayed-Release Tablets

BETWEEN:

Name: Eleanor DeLorme Sullivan, Ph.D., Director, Regulatory Affairs
Justin Victoria, President, Worldwide Regulatory Affairs
Phone: (610) 902-3105
Representing: Wyeth-Ayerst Laboratories

AND

Name: Lilia Talarico, M.D., Director
Steven Aurecchia, M.D., Deputy Director
Hugo Gallo-Torres M.D., Ph.D., GI Medical Team Leader
Liang Zhou, Ph.D., Chemistry Team Leader
Marie Kowblansky, Ph.D., Chemistry Reviewer
Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Draft Labeling; Loss on Drying Specification

BACKGROUND: NDA 20-987, Protonix (pantoprazole sodium) Delayed-Release Tablets was approvable on June 30, 1999 pending chemistry, biopharmaceutics, and labeling issues. The sponsor submitted their response to the approvable letter on July 30, 1999.

In response to the FDA's revised draft labeling, faxed to the sponsor on November 23, 1999, the sponsor submitted revised portions of the draft labeling (i.e. CLINICAL PHARMACOLOGY, Pharmacodynamics, *Enterochromaffin-Like (ECL) Cell Effects*; PRECAUTIONS, General; and PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility) on December 3, 1999. The Division made revisions to the December 3, 1999 revised portions of the draft labeling and faxed these to the sponsor on January 11, 2000. The sponsor requested a brief teleconference with the Division to discuss the draft labeling and the timing of the approval action. In preparation for this teleconference, the sponsor faxed to the Division, on January 19, 2000, proposed revisions to the PRECAUTIONS, General, subsection of the draft labeling as follows:

from: [ ]

to: "Pantoprazole is carcinogenic in rodents and caused rare types of gastrointestinal tumors in rodents. The relevance of these animal findings to human risk is unknown.

The safety and efficacy of PROTONIX for maintenance therapy (e.g. beyond 16 weeks) have not been established. Protonix is not indicated for maintenance therapy (see INDICATIONS AND USAGE)."

These revisions were reviewed by Drs. Talarico and Choudary.

TODAY'S CALL: Mr. Victoria said the sponsor concurred with the Division's revisions to the *Enterochromaffin-Like (ECL) Cell Effects* and the Carcinogenesis, Mutagenesis, Impairment of Fertility subsections of the draft labeling (faxed on January 11, 2000). However, under PRECAUTIONS, General, the sponsor proposes to separate the statement regarding carcinogenicity in rodents from the statements regarding maintenance therapy. Dr. Talarico said the statements in this subsection must remain in one paragraph because the carcinogenicity findings in rodents remain a safety concern and, in the absence of long-term safety data in humans, preclude the use of Protonix for maintenance therapy at this time. In response to the sponsor's question regarding a future supplement for maintenance therapy, Dr. Talarico said the PRECAUTIONS section of the labeling may be revised in that supplement, as appropriate. Mr. Victoria said he would relay the Agency's position to his upper management. Dr. Talarico emphasized that this is the Agency's final decision on this issue.

Regarding the proposal to add "in rodents" at the end of the sentence, "Pantoprazole is carcinogenic in rodents and caused rare types of gastrointestinal tumors," Dr. DeLorme Sullivan proposed the following revision to reduce redundancy: "In rodents, pantoprazole is carcinogenic and caused rare types of gastrointestinal tumors." Dr. Talarico said this was acceptable.

Dr. Kowblansky said the chemistry review is complete and the Agency recommends that the loss on drying (LOD) specification be extended from release throughout the expiry period. She noted that the International Conference on Harmonization (ICH) is adopting guidelines that will require this specification. Dr. Sullivan asked if the release specification of — must be maintained throughout expiry or if a higher specification may be proposed. Dr. Zhou said the sponsor may propose a slightly higher specification. The sponsor will discuss this issue internally and propose a new LOD specification.

[redacted]

Dr. Talarico said the Agency is proceeding with an approval action at this time.

/S/ 2/1/00

Maria R. Walsh, M.S.
Regulatory Project Manager

NDA 20-987

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole sodium sesquihydrate) Delayed-Release Tablets.

We also refer to your July 30, 1999 submission which includes your complete response to the June 30, 1999 approvable letter.

We are reviewing the chemistry section of your submission and have identified deficiencies in the Drug Master File (DMF) for the drug substance. We are hereby notifying you that a deficiency letter, dated November 23, 1999, has been issued to [redacted] regarding DMF [redacted] for pantoprazole sodium.

Per the user fee reauthorization agreements, the comments issued to the DMF holder do not reflect a final decision on the information reviewed in your application and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If the DMF holder chooses to respond to the issues raised in the deficiency letter during this review cycle, depending on the timing of their response, as per the user fee reauthorization agreements, we may or may not be able to consider their response prior to taking an action on your application during this review cycle.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

/S/

Liang Zhou, Ph.D.
Acting Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

WALSH

NOV - 8 1999

NDA 20-987

DISCIPLINE REVIEW LETTER

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DeLorme Sullivan:

Please refer to your June 30, 1998 new drug application for Protonix (pantoprazole sodium) Delayed-Release Tablets.

We also refer to your submission dated July 30, 1999 which constituted a complete response to our June 30, 1998 approvable letter.

Our reviews of the Chemistry and Biopharmaceutics sections of your submission are complete, and we have identified the following deficiencies:

Biopharmaceutics

Based on the data submitted, we recommend a paddle speed of 75 rpm with Q ——— in the drug product dissolution testing specification.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 443-0487.

Sincerely,

/S/

Liang Zhou, Ph.D.
Acting Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Archival NDA 20-987
HFD-180 Div. Files
HFD-180 M.Walsh
HFD-180 M.Kowblansky
L.Zhou
HFD-870 D.Udo
D.Lee
HFD-820 DNDC Division Director (only for CMC related issues)
DISTRICT OFFICE

Drafted by: M.Walsh 11/8/99
Initialed by: M.Kowblansky 11/8/99
L.Zhou 11/8/99
final: M.Walsh 11/8/99
filename: 20987911.IR

DISCIPLINE REVIEW LETTER (DR)

APPEARS THIS WAY
ON ORIGINAL

WASH

NDA 20-987

OCT 2 1 1999

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole sodium sesquihydrate) Delayed-Release Tablets .

We also refer to your submissions dated October 8 and 13, 1999 which included a draft report of the 28-day dose-ranging study in C57BL/6 mice and a revised protocol for the 26-week study in p53(+/-) heterozygous mice.

We have completed the review of your submission, consulted the Center's Executive Carcinogenicity Assessment Committee (CAC), and have the following recommendations regarding the 26-week carcinogenicity study with p53(+/-) transgenic mice:

1. The following doses should be used in the study:

   Pantoprazole: 62.5, 125, and 250 mg/kg/day
   Lansoprazole: 125, 360, and 900 mg/kg/day
   Omeprazole: 125, 360, and 900 mg/kg/day

2. We note that histological evaluation of tissues of all animals in the vehicle-control, positive control, and all pantoprazole treatment groups will be performed. However, such evaluation will be limited to the high dose lansoprazole and omeprazole treatment groups. Histopathologic examination of the corresponding mid and low dose groups should also be performed under any of the following circumstances:

   A. For any macroscopic findings in the low and mid dose groups for a given tissue, that tissue should be examined for all three dose groups.

   B. For an increase in the incidence of tumors (rare or common) in the high dose group for a tissue, even if not statistically significant, the next lower dose group should be examined.

   C. For an increase in tumors in an organ for a tumor type that should be analyzed across tissue sites as well as by tissue site (e.g. hemangiosarcoma, lymphoma, etc; see

McConnell et al, JNCI 76:283, 1986), all relevant tissues for that dose level and the next lower dose level should be examined.

D. For an excessive decrease in body weight or survival in the examined dose group, the lower dose groups should also be examined.

We note that given the limited experience with transgenic mouse models, the types of tumors that may need to be combined may not be adequately or completely described in the recommendations by McConnell et al.

2. Histopathology findings obtained from analyses of tissues by the study pathologist(s) and peer review pathologist(s) should be reported separately as well as the consensus findings from the study peer review.

3. We note that the comparator study drugs, lansoprazole and omeprazole, will be manufactured and supplied by Byk Gulden in Germany for use in the study. In the case of positive results with the comparator study drugs, you should compare the omeprazole and lansoprazole manufactured by Byk Gulden to the commercially available drug products, Prevacid and Prilosec, respectively, to determine potential differences in purity, impurities, and excipients and provide the results. We recommend you consider having an independent analytical testing laboratory conduct this comparative study.

If you have any questions, contact Maria R. Walsh, M.S., Project Manager, at (301) 827-8017.

Sincerely,

/S/ 10-21-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

WACSH

MEMORANDUM OF TELECON

DATE: October 14, 1999

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole sodium) Delayed-Release Tablets

BETWEEN:

Name: Eleanor DeLorme Sullivan, Ph.D., Regulatory Affairs
Phone: (610) 902-3105
Representing: Wyeth-Ayerst Laboratories

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Draft Report of the 28-day Dose-Ranging Study in C57BL/mice

BACKGROUND: NDA 20-987, Protonix (pantoprazole sodium) Delayed-Release Tablets was approvable on June 30, 1999. As part of a phase 4 commitment to conduct a 26-week carcinogenicity study in heterozygous p53 (+/-) transgenic mice, the sponsor submitted a draft report of a 28 day dose-ranging study in C57BL/6 mice for our review (per our July 12, 1999 information request letter) in an amendment dated October 1, 1999.

TODAY'S CALL: Per an October 14, 1999 e-mail from the Pharmacology Team Leader, Dr. Jasti Choudary, I called Ms. DeLorme Sullivan and asked her to provide the histopathology data on the dead or killed animals of the high dose group of pantoprazole and an assessment of the cause of death.

Ms. DeLorme Sullivan called me later today and relayed the following: Since all the animals in the high dose group died, it is clear that the maximum tolerated dose (MTD) was exceeded and therefore, histopathology on the animals was not done. Histopathology can be done (it would take two weeks to complete) but since there were no gross findings to suggest a cause of death (as is often the case in short-term studies), this data would not provide any useful information.

I told Ms. DeLorme Sullivan I would convey the above to Dr. Choudary and the clal was then concluded.

/S/ 10/14/99
Maria R. Walsh, M.S.
Regulatory Project Manager

APPEARS THIS WAY
ON ORIGINAL

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

WALSH

NDA 20-987

OCT 19 1999

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole sodium sesquihydrate) Delayed-Release Tablets.

We also refer to your July 30, 1999 submission which includes your complete response to the June 30, 1999 approvable letter.

We are reviewing the chemistry section of your submission and have identified deficiencies in the Drug Master File (DMF) for the drug substance. We are hereby notifying you that a deficiency letter, dated October 13, 1999, has been issued to ——— regarding DMF —— for pantoprazole sodium.

Per the user fee reauthorization agreements, the comments issued to the DMF holder do not reflect a final decision on the information reviewed in your application and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If the DMF holder chooses to respond to the issues raised in the deficiency letter during this review cycle, depending on the timing of their response, as per the user fee reauthorization agreements, we may or may not be able to consider their response prior to taking an action on your application during this review cycle.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely,

/S/

Liang Zhou, Ph.D.
Acting Chemistry Team Leader for the
Division of Gastrointestinal and Coagulation Drug Products, (HFD-180)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

WALSH

MEMORANDUM OF TELECON

DATE: October 12, 1999

APPLICATION NUMBER: NDA 20-987;
Protonix (pantoprazole sodium) Delayed-Release Tablets

BETWEEN:

Name: Eleanor DeLorme Sullivan, Ph.D., Regulatory Affairs
Phone: (610) 902-3105
Representing: Wyeth-Ayerst Laboratories

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Draft report for a 28-day dose-ranging study in C57BL/6 mice - Information request

BACKGROUND: NDA 20-987, Protonix (pantoprazole sodium) Delayed-Release Tablets was approvable on June 30, 1999. As part of a phase 4 commitment to conduct a 26-week carcinogenicity study in heterozygous p53 (+/-) transgenic mice, the sponsor submitted a draft report of a 28 day dose-ranging study in C57Bl/6 mice for our review (per our July 12, 1999 information request letter) in an amendment dated October 1, 1999.

TODAY'S CALL: Per the October 8, 1999 memo from the pharmacology reviewer, Dr. Timothy Robison, I called Ms. DeLorme Sullivan and asked her to provide the following information regarding the dose-ranging study in mice (Study # 98103):

1. Specify the sources of omeprazole and lansoprazole used in the study and how they compare to the drugs in clinical use.

2. Provide the findings of each pathologist for analysis of study tissues and the consensus results obtained from the two pathologists.

Ms. DeLorme Sullivan said she would provide this information via fax as soon as possible to be followed by hard copy. The call was then concluded.

(S) 10/12/99

Maria R. Walsh, M.S.
Regulatory Project Manager

WALSH

NDA 20-987

AUG 17 1999

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DeLorme Sullivan:

We acknowledge receipt on August 3, 1999 of your July 30, 1999 resubmission to your new drug application (NDA) for Protonix (pantoprazole sodium sesquihydrate) Delayed-Release Tablets.

This resubmission contains additional chemistry, biopharmaceutics, and labeling information submitted in response to our June 30, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is February 3, 2000.

If you have any questions, contact me at (301) 443-8017.

Sincerely,

/S/ 8/17/99

Maria R. Walsh, M.S.
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Walsh

NDA 20-987

JUL 12 1999

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole sodium sequihydrate) Delayed-Release Tablets.

We also refer to your submission, dated June 21, 1999, containing your draft protocol for a 26-week carcinogenicity study in p53 mice.

We have completed our review of your submission and have the following comments.

1. A 4-week oral dose range finding toxicity study should be conducted for pantoprazole and the proposed reference drugs in C57BL/6 mice to identify maximum doses (MTD) based on toxicity endpoints. The conduct of the study should be in general accord with the Final Protocol dated June 10, 1997. The toxicity endpoints should include histopathology evaluation of all tissues and any gross lesions from mice of the control and all treatment groups. The pH of the dosing solutions should be adjusted to prevent acid-induced degradation of the test substances in the stomach.

2. In the proposed 26-week carcinogenicity study in transgenic p53(+/-) mice, histopathological evaluations should be conducted for 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.

3. For the assessment of the outcome of the p53(+/-) mouse carcinogenicity study, statistical procedures used for 2-year carcinogencity studies may be considered. However, the assessment has to rely more on the qualitative findings in individual dose groups.

4. Please provide a revised draft protocol for the 26-week carcinogenicity study in transgenic p53(+/-) mice, along with the report of the completed 4-week dose range finding study in C57BL/6 mice for further comments and advice.

If you have any questions, contact Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-0487.

Sincerely,

7-12-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-987
HFD-180/Div. Files
HFD-180/M.Walsh
HFD-180/J.Choudary
HFD-024/J.DeGeorge

Drafted by: M.Walsh 7/8/99
Initialed by: J.Choudary 7/12/99
L.Talarico 7/12/99
final: M.Walsh 7/12/99
filename:

INFORMATION REQUEST (IR)

walsh

MEMORANDUM OF TELECON

DATE: June 16, 1999

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole sodium) Delayed-release Tablets

BETWEEN:

Name: Dr. Eleanor DeLorme Sullivan
Phone: (610) 902-3728
Representing: Wyeth-Ayerst Laboratories

AND

Name: Ms. Bronwyn Collier
Office of Drug Evaluation III, HFD-103

SUBJECT: Phase 4 commitment

Background: Wyeth-Ayerst had been requested to commit to conducting a 26-week study in P53 deficient transgenic mice to evaluate further the potential for tumorigenicity with long term exposure of pantoprazole. The commitment was discussed during a June 11, 1999, telephone conference with the applicant. Following the telephone conference, Wyeth-Ayerst submitted, on June 14, 1999, a proposal for submission of data to a future supplement for long-term use of pantoprazole and the requested phase 4 commitment to the current NDA.

Call: I asked for clarification on one point concerning the phase 4 commitment stated in the June 14, 1999, letter, "Submit a protocol for the 26-week study and a report of the dose range study (as appropriate) as soon as possible for FDA review." I explained that we would like to be able to review the protocol within a time frame that would allow the P53 mouse study to begin prior to anticipated approval of the NDA. Dr. DeLorme said that they would submit the protocol in a week. However, the doses to be used in the study will not be identified in the protocol until the dose-ranging study can be completed.

We also discussed the importance of conducting the study, to the extent possible, independently from Wyeth-Ayerst oversight. Dr. DeLorme said these precautions are part of their routine but that they would address it in the protocol.

I informed Dr. DeLorme that the biopharm review was nearing completion and that there would probably be no additional phase 4 commitment requests from that discipline.

/S/ 6/16/99

Bronwyn Collier, ADRA ODE III

WALSH

MEMORANDUM OF TELECON

DATE: June 10, 1999

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole sodium) Delayed-Release Tablets

BETWEEN:

Name: Eleanor DeLorme Sullivan, Ph.D., Regulatory Affairs
Phone: (610) 902-3105
Representing: Wyeth-Ayerst Laboratories

AND

Name: Maria R. Walsh, M.S., Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for Phase 4 Commitment

BACKGROUND: NDA 20-987 was submitted on June 30, 1998 for the use of pantoprazole for the short-term treatment of gastroesophageal reflux disease (GERD). Issues concerning carcinogenicity and genotoxicity were identified during the review of the preclinical data. Upon further review of the data by the Office of Drug Evaluation (ODE) III, it was decided that the sponsor should be asked to conduct a 26-week study in p53 transgenic mice to further evaluate the potential for tumorigenicity with long-term exposure of pantoprazole as a phase 4 commitment.

TODAY'S CALL: I called Ms. DeLorme Sullivan and asked her if the sponsor would agree to the following phase 4 commitments:

A 26-week carcinogenicity study in heterozygous p53 (+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose range finding study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints.

The protocol for the carcinogenicity study should be submitted along with the report of the dose ranging study for the Agency's review as soon as possible.

The carcinogenicity study should be initiated as soon as the sponsor receives the Agency's comments on the protocol.

The studies should be completed and the study reports should be submitted within one year of initiation.

After conferring with her colleagues, Ms. DeLorme Sullivan said the sponsor agrees to the above phase 4 commitments. The sponsor will submit these commitments in writing to the NDA.

She requested a teleconference with Dr. Florence Houn, Director, ODE III to discuss this issue further. I told Ms. DeLorme Sullivan that I would arrange a teleconference and inform her of the date and time.

The call was then concluded.

/1/ 7/14/99
Maria R. Walsh, M.S.
Regulatory Project Manager

cc: Original NDA 20-987
HFD-180/Div. File
HFD-180/M.Walsh
HFD-180/L.Talarico
H.Gallo-Torres
J.Choudary
filename:

TELECON

CSO/Model

NDA 20-987

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

OCT - 6 1998

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole) 40 mg Enteric-Coated Tablets.

We are reviewing the pharmacology section of your submission. For the 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)," we note that 24 rats/sex/group were used. However, complete gross pathological and histopathological examinations were only performed for 20 rats/sex/group in both studies. Please provide the gross pathological and histopathological examinations for the following animals in these studies.

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

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

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

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

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact me at (301) 443-0487.

Sincerely,

10/5/98

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-987

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

SEP 28 1998

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole sodium) 40 mg Enteric-Coated Tablets.

We are reviewing the pharmacology section of your submission and request that you submit a statistical analysis of the animal carcinogenicity data according to the attached draft guidance document entitled, "Statistical Aspects of Design, Analysis, and Interpretation of Animal Carcinogenicity Studies."

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, contact me at (301) 443-0487.

Sincerely,

9/28/98

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

CSO/Walsh

NDA 20-987

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, Ph.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

SEP - 1 1998

Dear Dr. DeLorme Sullivan:

Please refer to your pending June 30, 1998 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Protonix (pantoprazole) 40 mg Enteric-Coated Tablets.

We are reviewing the clinical statistical section of your submission and have the following information requests:

1. Please provide Cochran-Mantel-Haenszel (and Breslow-Day) tests for the pivotal trials stratified by center.

2. Please provide exact odds ratio test and Zelen's test for the pivotal trials stratified by center.

3. Please provide exact odds ratio tests and Zelen's test for the pivotal trials stratifying by gender, *H. pylori* status, etc., paralleling the Cochran-Mantel-Haenszel analyses contained in the application. In addition, please indicate the location of the Cochran-Mantel-Haenszel analyses in the application.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact me at (301) 443-0487.

Sincerely,

151 9/1/98

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-987
HFD-180/Div. Files
HFD-180/PM/M.Walsh
HFD-720/A.Sankoh
F.Harrison
DISTRICT OFFICE

Drafted by: M.Walsh 8/26/98
Initialed by: K.Johnson 8/31/98
F.Harrison 8/31/98
A.Sankoh 8/31/98
final: M.Walsh 9/1/98
filename: [redacted]

INFORMATION REQUEST (IR)