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 June 30, 1998 new drug application for Protonix (pantoprazole sodium) 40 mg Enteric-Coated Tablets.

We also refer to your August 20, 1998 letter in which you presented various options regarding the submission of the safety data from Protocol Nos. 302 and 303 (GERD maintenance of healing studies) in a safety update for NDA 20-987.

We have completed our review of your correspondence. We request that you submit one safety update by the end of February 1999 which will include new safety data from the Byk Gulden studies as well as new safety data from Protocol Nos. 302 and 303. We understand that the safety data from Protocol Nos. 302 and 303 will include only the data generated from an interim unblinded safety analysis of a majority of the patients, which you propose to perform in early 1999.

Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Please submit this information by the end of February, 1999 as stated in your August 20, 1998 letter.

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

Sincerely,

(5) 9-1-98

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
DISTRICT OFFICE

Drafted by: M.Walsh 8/27/98
Initialed by: H.Gallo-Torres 8/27/98
L.Talarico 8/27/98
final: M.Walsh 9/1/98
filename: [redacted]

INFORMATION REQUEST (IR)

N80/Walsh

MEMORANDUM OF TELECON

DATE: August 25, 1998

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole) 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.
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Request for information re: placebo/facilities/carcinogenicity study

BACKGROUND: The sponsor submitted NDA 20-987, Protonix (pantoprazole) Tablets, on June 30, 1998. The 45-day filing/planning meeting was held on August 25, 1998. Several requests for information emerged prior to and during that meeting as discussed below.

TODAY'S CALL: I called Dr. DeLorme Sullivan and requested that an additional hard copy of the Fischer rat carcinogenicity study be provided for the statistical reviewer. She agreed to provide copies of the pertinent volumes. (The pharmacologist's copy of the carcinogenicity data on diskette will be provided to Dr. Harrison by Dr. Robison) .

I asked Dr. DeLorme-Sullivan if information on the composition of the placebo (qualitative and quantitative) was included in the NDA and if so, to please assist us in locating it. She replied that this information was submitted to the IND only. She offered to fax to us this information as soon as possible and follow-up with a hard copy to the NDA. I said this was acceptable.

The call was then concluded.

(51

8/26/98

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

CC
M.U. ed.

NDA 20-987

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

JUL - 8 1998

Dear Dr. DeLorme Sullivan:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Protonix (pantoprazole) 40 mg Enteric-Coated Tablets

Therapeutic Classification: Standard (S)

Date of Application: June 30, 1998

Date of Receipt: June 30, 1998

Our Reference Number: 20-987

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 28, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 30, 1999.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

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

Sincerely,

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

cc:
Archival NDA 20-987
HFD-180/Div. Files
HFD-180/M.Walsh
DISTRICT OFFICE

final: M.Walsh 7/7/98 (5) 7/7/98
filename: [redacted]

ACKNOWLEDGEMENT (AC)

CAO/ Walsh

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 24, 1998
Time: 1:00 p.m. - 2:00 p.m.
Location: Conference Room 6B-45, Parklawn Building

Application: NDA 20-987; Protonix (pantoprazole sodium) 40 mg Enteric-Coated Tablets

Type of Meeting: 45-day filing meeting

Meeting Chair: Lilia Talarico, M.D., Director

Meeting Recorder: Maria R. Walsh, M.S., Regulatory Project Manager

Attendees:

Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
Lilia Talarico, M.D., Director
Hugo Gallo-Torres, M.D., Ph.D., GI Team Leader
Eric Duffy, Ph.D., Chemistry Team Leader
Marie Kowblansky, Ph.D., Chemistry Reviewer
Jasti Choudary, Ph.D., B.V.Sc., Pharmacology Team Leader
Timothy Robison, Ph.D., Pharmacology Reviewer

Division of Biometrics III (HFD-720)
A.J. Sankoh, Ph.D., Biostatistics Team Leader
Ferrin Harrison, Ph.D., Biostatistics Reviewer

Division of Pharmaceutical Evaluation II (HFD-870)
John Hunt, Biopharmaceutics Team Leader
Alfredo Sancho, Ph.D., Biopharmaceutics Reviewer

Division of Scientific Investigations (HFD-340)
Michael Skelly, Good Laboratory Practices and Bioequivalence Branch

Background: Wyeth-Ayerst Laboratories submitted NDA 20-987 for Protonix (pantoprazole sodium) 40 mg Enteric-Coated Tablets, a proton pump inhibitor, on June 30, 1998, for the following proposed indication: short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD).

Meeting:

1. **Administrative**

Filing issues: None

Administrative issues/requests: None

2. **Chemistry, Manufacturing, and Controls**

Filing issues: None

Scientific issues/requests:

A. A categorical exclusion for an environmental assessment was claimed and found acceptable.

3. **Nonclinical Pharmacology**

Filing issues: None

Scientific issues/requests: Regarding the carcinogenicity studies, only the Fischer rat study should be reviewed by the statistician since Dr. Wen-Jen Chen has already reviewed the other carcinogenicity studies under the IND. Dr. Robison will review the tumor promotion studies to identify if any information is needed.

4. **Biopharmaceutics**

Filing issues:

If the to-be-marketed tablets were not used in the pivotal trials, then a detailed description of the active and inactive ingredients of the tablets used in these studies and comparison with the to-be marketed tablet should be provided.

Upon discussion, it was determined that several formulations were used in the clinical studies and that a description of the active and inactive ingredients of these formulations is contained in the CMC section. Dr. Sancho will examine the bioequivalency studies to determine whether all the linkages between the various formulations and the to-be-marketed product are contained in the application.

(Post-meeting note: All the required information is present in the NDA and the application may be filed from a biopharmaceutics standpoint).

Scientific issues/requests:

5. **Statistics**

Filing issues: None

Scientific issues/requests: None

6. **Clinical**

Filing issues: None

Scientific issues/requests: The sponsor has not conducted any studies in the pediatric population. The Agency will not ask the sponsor to conduct such studies at this time because it is not clear whether this drug is appropriate for use in the pediatric population due to its preclinical profile.

7. **DSI**

Dr. Gallo-Torres will provide a list of sites to the project manager for consultation to DSI for clinical site investigation.

Dr. Sancho will provide a list of sites to the project manager for consultation to DSI for biopharm site investigation .

(Post-meeting note: No biopharm sites were identified).

8. **Goal Date/Review Due Dates:** For the 10-month due date of April 30, 1999, the final reviews should be completed by February 19, 1999.

Conclusion

NDA 20-987 will be filed on August 28, 1998. A team meeting will be scheduled in December 1998 to discuss the progress of the reviews.

Minutes Preparer: ISI 10/19/98

Chair Concurrence: ISI 10-19-98

cc: Original NDA
HFD-180/Div. Files
HFD-180/Meeting Minutes files
HFD-180/PM/M.Walsh
HFD-180/H.Gallo-Torres
M.Kowblansky
E.Duffy
T.Robison
J.Choudary
HFD-720/F.Harrison
A.Sankoh
HFD-870/A.Sancho
J.Hunt
Drafted by: M.Walsh 9/1/98
Initialed by: E.Duffy 9/3/98
J.Choudary 9/3/98
D.Lee 9/9/98
A.Sancho 10/18/98
H.Gallo-Torres 9/3/98
L.Talarico 9/8/98
final: M.Walsh 10/19/98
filename: _____

MEETING MINUTES

walsh

NDA 20-987

Wyeth-Ayerst Laboratories
Attention: Eleanor DeLorme Sullivan, PhD
Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

JUL 12 1999

Dear Dr. 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) Delayed-Release Capsules.

We also refer to your submissions dated April 26, May 11, and June 2, 1999.

We have completed our review of the pharmacology section(s) of your submission and have the following comments and information requests:

Regarding the April 26, and May 11, 1999 amendments:

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

2. For the purposes of quantitation, you expressed all results as adducts per 10^8 nucleotides. Please confirm whether the units are relative adduct labeling (RAL).

3. Spot 1 in Figure 4 (Volume 1.077, Page 35) is reported as a background indigenous spot; however, it might be an artifact due to the fact that it is not observed in Figure 4 panel E.

Please clarify whether controls were conducted in the absence of DNA and/or DNA from another source (i.e., calf thymus, salmon sperm).

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

Regarding the June 2, 1999 amendment, the first-generation photocopies of ——— of the ^{32}P-Postlabeling study offer no additional information pertaining to the interpretation of study results as compared to photocopies submitted on April 26, 1999. There is no need to continue resubmitting this material. We suggest you consider repeating this study. Each sample should be processed with and without the nuclease P1 enhancement procedure prior to ^{32}P-labeling and subsequent ——— Background indigenous spots should be appropriately characterized and units of quantitation should be justified.

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

Sincerely,

/S/ 7-5-99

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/Choudary
Drafted by: kj/June 28, 1999
Initialed by: Jchoudary 6/29/99
filename: ———

INFORMATION REQUEST (IR)

Printed by Maria Walsh

Electronic Mail Message

itivity: COMPANY CONFIDENTIAL

Date: 07-Jan-2000 10:07am
From: Timothy Robison
ROBISONT
Dept: HFD-180 PKLN 6B45
Tel No: 301-827-7310 FAX 301-443-9285

TO: See Below
Subject: Pharm/Tox sections of Protonix label (Suggested change in genotoxicity paragraph).

We intended to respond to Dr. Morse's draft of January 5, 2000 with our comments regarding the labeling for pantoprazole; however, we were somewhat late due to time constraints. We believe the paragraph regarding genotoxicity assays conducted with pantoprazole requires some modification as described in the attachment. Thank you.

Jasti Choudary
Tim Robison

Distribution:

TO: Florence Houn	(HOUNF)
TO: Lillie Talarico	(TALARICO)
TO: Steven Aurecchia	(AURECCHIA)
TO: Hugo Gallo Torres	(GALLOTORRESH)
TO: Maria Walsh	(WALSH)
TO: Joseph DeGeorge	(DEGEORGE)
TO: David Morse (CDER/DAVDP)	(MORSED)
Jasti Choudary	(CHOUDARY)
Timothy Robison	(ROBISONT)

APPEARS THIS WAY
ON ORIGINAL

We intended to respond to Dr. Morse's draft of January 5, 2000 with our comments regarding the labeling for pantoprazole; however, we were somewhat late due to time constraints. We believe the paragraph regarding genotoxicity assays conducted with pantoprazole requires some modification as described below.

Original paragraph:

[ ]

Evaluation:

The first sentence appears to inadvertently imply that clastogenic effects were found with the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay. This assay detects mutagenic effects. The sentence regarding the [redacted] was completely deleted. The sponsor in their version dated December 3, 1999 stated "Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay." This sentence should be retained in the labeling.

Revised paragraph:

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays and in one of two *in vivo* mouse micronucleus tests for clastogenic effects and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were obtained in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the ~~*in vitro*~~ AS52/GPT mammalian cell-forward gene mutation assay, and the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells.

Dr. Morse's version is reproduced below with the above suggested revision in the paragraph concerning genotoxicity findings.

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (~~24~~ months) to pantoprazole at doses of 0.5 to 200 mg/kg/day, resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE) cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high

density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin levels produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

[redacted]

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole has not been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed once every other day in these patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a mg/m^2 basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and an hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on

body surface area adjustment. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays and in one of two *in vivo* mouse micronucleus tests for clastogenic effects and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were obtained in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, and the *in vitro* thymidine-kinase mutation test with mouse lymphoma L5178Y cells.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Memorandum

Date: 6 January 2000

From: David E. Morse, Ph.D.
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Tim Robison, Ph.D., Pharm./Tox., DGCDP (HFD-180)

Subject: NDA 20-987
PROTONIX® (pantoprazole sodium) Delayed Release Tablets
Review of Pharm./Tox. Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Label Review of NDA 20-987, written by Jasti Choudary, B.V.Sc., Ph.D., dated 28 Dec., 1999.
2. Wyeth-Ayerst draft product labeling, dated 3 Dec. 1999.

Related Product Labels:

3. PRILOSEC® (omeprazole) Delayed-Release Capsules
4. PREVACID® (lansoprazole) Delayed-Release Capsules
5. ACIPHEX® (rabeprazole sodium) Delayed-Release Tablets

II. Recommendations for Product Labeling

(A clean copy of the text for the edited P/T sections of the product label are presented first, followed by an annotated copy of the revisions.)

Enterochromaffin-Like (ECL) Cell Effects

In 39 patients treated with oral pantoprazole 40 mg to 240 mg daily (majority receiving 40 mg to 80 mg) for up to 5 years, there was a moderate increase in ECL-cell density starting after the first year of use which appeared to plateau after 4 years.

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day, resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE) cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin levels produced by proton pump inhibitors. However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1

female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General

Symptomatic response to therapy with pantoprazole does not preclude the presence of gastric malignancy.

The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. Pantoprazole is carcinogenic in rodents and caused rare types of gastrointestinal tumors. The relevance of these animal findings to human risk is unknown. PROTONIX is not indicated for maintenance therapy (see **INDICATIONS AND USAGE**).

No dosage adjustment is necessary in patients with mild or moderate hepatic impairment. The pharmacokinetics of pantoprazole has not been well characterized in patients with severe hepatic impairment. Therefore, the potential for modest drug accumulation (≤21%) when dosed once daily needs to be weighed against the potential for reduced acid control when dosed once every other day in these patients.

Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 24-month carcinogenicity study, Sprague-Dawley rats were treated orally with doses of 0.5 to 200 mg/kg/day, about 0.1 to 40 times the exposure on a body surface (mg/m^2) basis, of a 50-kg person dosed at 40 mg/day. In the gastric fundus, treatment at 0.5 to 200 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors in a dose-related manner. In the forestomach, treatment at 50 and 200 mg/kg/day (about 10 and 40 times the recommended human dose on a mg/m^2 basis) produced benign squamous cell papillomas and malignant squamous cell carcinomas. Rare gastrointestinal tumors associated with pantoprazole treatment included an adenocarcinoma of the duodenum at 50 mg/kg/day, and benign polyps and adenocarcinomas of the gastric fundus at 200 mg/kg/day. In the liver, treatment at 0.5 to 200 mg/kg/day produced dose-related increases in the incidences of hepatocellular adenomas and carcinomas. In the thyroid gland, treatment at 200 mg/kg/day produced increased incidences of follicular cell adenomas and carcinomas for both male and female rats.

Sporadic occurrences of hepatocellular adenomas and an hepatocellular carcinoma were observed in Sprague-Dawley rats exposed to pantoprazole in 6-month and 12-month toxicity studies.

In a 24-month carcinogenicity study, Fischer 344 rats were treated orally with doses of 5 to 50 mg/kg/day, approximately 1 to 10 times the recommended human dose based on body surface area adjustment. In the gastric fundus, treatment at 5 to 50 mg/kg/day produced enterochromaffin-like (ECL) cell hyperplasia and benign and malignant neuroendocrine cell tumors. Dose selection for this study may not have been adequate to comprehensively evaluate the carcinogenic potential of pantoprazole.

In a 24-month carcinogenicity study, B6C3F1 mice were treated orally with doses of 5 to 150 mg/kg/day, 0.5 to 15 times the recommended human dose based on body surface area. In the liver, treatment at 150 mg/kg/day produced increased incidences of hepatocellular adenomas and carcinomas in female mice. Treatment at 5 to 150 mg/kg/day also produced gastric fundic ECL cell hyperplasia.

Pantoprazole was positive for clastogenic effects in the *in vitro* human lymphocyte chromosomal aberration assays, the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay, and in one of two *in vivo* mouse micronucleus tests. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* AS52/GPT mammalian cell-forward gene mutation assay, or the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells.

Pantoprazole at oral doses up to 500 mg/kg/day in male rats (98 times the recommended human dose based on body surface area) and 450 mg/kg/day in female rats (88 times the recommended human dose based on body surface area) was found to have no effect on fertility and reproductive performance.

Annotated Revisions to Original Text

Enterochromaffin-Like (ECL) Cell Effects

2 PAGE(S) REDACTED

Draft

Labeling

III. Summary

A review of the materials referenced in item "I" of this document suggests the need for several editorial and content changes to the draft Pharm./Tox. Labeling for PROTONIX® (pantoprazole sodium. NDA 20-987). Specific suggestions for changes to the product label are presented in item "II" (a clean copy of the text for the edited P/T sections of the product label is presented first, followed by an annotated copy of the suggested revisions.)

MEMORANDUM

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

DATE: December 28, 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 December 3, 1999 - Sponsor's Revised Draft Labeling.

TO: NDA 20,987

The Agency provided a revised version of draft labeling dated November 23, 1999 to the sponsor in response to the sponsor's revised version dated July 30, 1999. Agency's revised version (dated November 23, 1999) was provided to the sponsor to facilitate the discussions at the meeting on November 29, 1999. Subsequent to the meeting, sponsor submitted the present amendment (dated December 3, 1999) with further changes presumably in accord with a teleconference of December 1, 1999 between the representatives of the Division and the sponsor. The changes relate only to portions of labeling most of which are based on findings in the preclinical studies. These revisions are piecemeal, and they are not well-founded. Nevertheless, they are reviewed below. They are arranged in the following order: FDA REVISED VERSION 11/23/99, Wyeth-Ayerst's REVISION 12/3/99, evaluation, recommendation and FDA final draft. The specific portions are: I. Enterochromaffin-Like (ECL) Cell Effects under subsection - Pharmacodynamics of CLINICAL PHARMACOLOGY section and II. General subsection of PRECAUTIONS Section and III. Carcinogenesis, Mutagenesis and Impairment of Fertility subsection of PRECAUTIONS section.

12 PAGE(S) REDACTED

Draft

Labeling

[redacted]

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

cc:
NDA
HFD-180
HFD-181/CSO, Ms. Walsh
HFD-180/Dr. Choudary
HFD-180/Dr. Robison
HFD-024/Dr. DeGeorge

JBC/hw/12/29/99

APPEARS THIS WAY
ON ORIGINAL