WALSH

MEMORANDUM OF TELECON

DATE: June 9, 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: Histopathology slides for NCTR

BACKGROUND: NDA 20-987 was submitted June 30, 1998 for the use of pantoprazole tablets 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 [redacted] and the Office of Drug Evaluation (ODE) III, the sponsor was asked to submit the histopathology slides of the animals with leukemia in the Fischer rat carcinogenicity study for review by the National Center for Toxicological Research (NCTR).

TODAY'S CALL: Per Dr. Jasti Choudary, Pharmacology Team Leader, HFD-180, I called Ms. DeLorme Sullivan and relayed that she should contact Dr. William Witt of NCTR at (870) 543-7949 for instructions regarding the submission of the histopathology slides for review. In addition, I informed Ms. DeLorme Sullivan that I would be faxing a list of additional slides/tissues that should be submitted to the NCTR for review (attached).

The call was then concluded.

/S/ 7/14/99

Maria R. Walsh
Regulatory Project Manager

Attachment

WALSH

MEMORANDUM OF TELECON

DATE: July 28, 1999

APPLICATION NUMBER: NDA 20-987 and IND [redacted]
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: Additional question re: phase 4 commitment (p53 transgenic mouse study)

BACKGROUND: NDA 20-987 was approvable on June 30, 1999 for the short-term treatment of erosive esophagitis. The sponsor agreed to conduct a 26-week carcinogenicity study in heterozygous p53 (+/-) mice with dose selection based on a 4-week dose ranging study in C57BL/6 mice as a phase 4 commitment. On July 21, 1999, the sponsor faxed to the Division a set of three questions regarding this commitment. The Division's recommendations were communicated to the sponsor in a July 27, 1999 teleconference between Ms. Walsh and Ms. DeLorme Sullivan.

TODAY'S CALL: Ms. DeLorme Sullivan called me with an additional question regarding the studies to be conducted as a phase 4 commitment. The sponsor plans to buffer the solution dosed to all animals (reference drugs and vehicle) to a pH level of 10.5 for both the dose ranging and p53 mouse studies. Is this acceptable?

After conferring with Dr. Jasti Choudary, Pharmacology Team Leader, I relayed to Ms. DeLorme Sullivan that although the proposed pH of 10.5 is acceptable, a pH of 8-10 is preferred. The call was then concluded.

7/28/99

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

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MEMORANDUM OF TELECON

DATE: June 8, 1999

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole sodium) Enteric-Coated Tablets

BETWEEN:

Name: Eleanor DeLorme Sullivan, Ph.D.
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: Submission of histopathology slides

BACKGROUND: NDA 20-987 was submitted June 30, 1998 and is pending an action. The sponsor submitted an amendment, dated June 2, 1999, [redacted] The sponsor proposes to submit histopathology slides of those animals in the Fisher rat carcinogenicity study diagnosed with granulocytic leukemia or large granular lymphocyte leukemia. The sponsor also proposes to submit histopathology slides of specific tumors in the Sprague-Dawley rat carcinogenicity study that were peer reviewed.

Per Dr. Choudary, I instructed Ms. DeLorme to call Dr. William Witt of the National Center for Toxicological Research (NCTR) at (870) 543-7949 or (870) 543-7514 and ask him how to submit the slides directly to the NCTR for review. After verifying the name and number given, the call was concluded.

151 6/8/99

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

CSO/Walsh

NDA 20-987

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

APR 2 9 1999

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) Enteric-Coated Tablets.

We are reviewing the Pharmacology section of your submission and have the following information requests regarding the Fischer rat carcinogenicity study (Study No. KR0143) and your statistical analysis:

1. Please clarify the number of animals per group in the study that were examined for granulocytic leukemia. If a reanalysis of the incidence of granulocytic leukemia was performed in treatment groups after the original report, please provide information regarding the testing facility, study dates, GLP compliance, and procedures used.

2. Please provide the spontaneous tumor incidences for Fisher 344 rats in the testing facility over the period of 1990 to 1995.

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 Maria R. Walsh, Regulatory Project Manager, at (301) 443-8017.

Sincerely,

/S/ 4/28/99

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/M.Walsh
HFD-180/J.Choudary

Drafted by: M.Walsh 4/27/99
Initialed by: J.Choudary 4/27/99
K.Johnson 4/28/99
final: M.Walsh 4/28/99
filename: [redacted]

INFORMATION REQUEST (IR)

CSO/Walsh

NDA 20-987

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

APR 28 1999

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) Enteric-Coated Tablets.

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 April 23, 1999, has been issued to ——— regarding DMF ——— for pantoprazole sesquihydrate.

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,

Eric P. Duffy, Ph.D.
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

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information

CSO/Wu-Ko

NDA 20-987

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

APR 13 [illegible]

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. We note that the description of methodology and presentation of results with regard to ^{32}P-Postlabeling Studies in GTR-32977 (Vol. 1.077) is incomplete and we have the following information requests:

1. Please provide a detailed description of methodology.

2. Please provide copies of all _____ produced in each experiment with regard to results.

3. Please identify all adducts in each sample. 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.

4. Please provide the results for each chromatography system. with either butanol extraction or Nuclease P1 enhancement. separately.

5. Please provide the results with tamoxifen. lansoprazole. omeprazole. and pantoprazole separately.

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. please contact Maria R. Walsh. Regulatory Project Manager. at (301) 443-8017.

Sincerely.

/S/ 4/13/99

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/M.Walsh
HFD-180/J.Choudary

Drafted by: M.Walsh 4/12/99
Initialed by: J.Choudary 4/12/99
K.Johnson 4/13/99
final: M.Walsh 4/13/99
filename: [redacted]

INFORMATION REQUEST (IR)

MEMORANDUM OF TELECON

DATE: March 1, 1999

APPLICATION NUMBER: NDA 20-987; Protonix (pantoprazole sodium) 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: Clinical information requests

BACKGROUND: NDA 20-987, Protonix (pantoprazole sodium) Tablets, submitted by the sponsor on June 30, 1998 for the short-term treatment of erosive esophagitis, is currently under review. Per Dr. Hugo Gallo-Torres, on February 18, 1999, I called Ms. DeLorme with the following information requests.

- Please specify the location of the rationale for testing the 20 and 40 mg doses in the clinical trials.

- Were intra-esophageal pH measurements performed? If so, please specify the location of these data in the application.

- Are there any other studies comparing pantoprazole 40 mg qd with nizatidine 150 mg bid in erosive esophagitis?

Ms. DeLorme Sullivan replied that she will check into the first two requests. She confirmed that no other studies comparing pantoprazole with nizatidine were performed. She added that Byk Gulden might have comparator studies with other H2 blockers.

I also asked Ms. DeLorme Sullivan to submit a copy of the proposed labeling on diskette in Word 97 format. She said she could submit this in Word 95, version 7.

TODAY'S CALL: I called Ms. DeLorme Sullivan today regarding another matter and she provided the following answers to the above information requests:

- The rationale for testing the 20 mg and 40 mg doses in the clinical trials can be found in the dose selection section in Vol. 1.240. Briefly, the following represents the rationale: the marketed dose for GERD in Europe is 40 mg; gastric acid secretion is optimally decreased with the 40 mg dose; and a lower dose was

included in Study 301 because Byk Gulden had evidence that 20 mg may be effective in GERD. However, this study did not include severe disease.

- Intra-esophageal pH measurements were performed in Byk Gulden's Study 29713, located in Vol. 1.253.

- No other studies comparing pantoprazole and nizatidine have been completed or planned.

Ms. DeLorme Sullivan said the above information will be sent in writing to the NDA. The call was then concluded.

/s/ 3/1/99
Maria R. Walsh, M.S.
Regulatory Project Manager

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

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