CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-987

ADMINISTRATIVE DOCUMENTS

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20987/000
Stamp: 30-JUN-1998
Regulatory Due: 03-FEB-2000
Applicant: WYETH AYERST LABS
145 KING OF PRUSSIA RD
RADNOR, PA 190874288
Priority: 1S
Org Code: 180

Action Goal: 03-FEB-2000
District Goal: 01-MAR-1999
Brand Name: PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
Estab. Name:
Generic Name: PANTOPRAZOLE SODIUM

Dosage Form: (DELAYED RELEASE TABLET
Strength: 40 MG

Application Comment:
FDA Contacts: M. WALSH (HFD-180) 301-827-7310 , Project Manager
M. KOWBLANSKY (HFD-180) 301-827-7310 , Review Chemist
E. DUFFY (HFD-150) 301-594-5765 , Team Leader

Overall Recommendation: ACCEPTABLE on 05-FEB-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: 2650135
AYERST WYETH PHARMACEUTICALS
STATE RD 3 KM 142.1
GUAYAMA, PR 00784

DMF No: AADA:
Responsibilities: FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: TCT OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUL-1998				WALSH
OC RECOMMENDATION	03-AUG-1998			ACCEPTABLE BASED ON PROFILE	DAMBROGIOJ

ACCEPTABLE BASED ON PROFILE CLASS CODE TCM. ONLY PKG AND TESTING.

Establishment: 9611662
BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH
ROBERT BOSCH STRASSE 8
SINGEN, , GM D-78224

DMF No: AADA:
Responsibilities: DRUG SUBSTANCE MANUFACTURER
DRUG SUBSTANCE RELEASE TESTER
DRUG SUBSTANCE STABILITY TESTER
Profile: CSN OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JUL-1998				WALSH
SUBMITTED TO DO	03-AUG-1998	GMP			DAMBROGIOJ
ASSIGNED INSPECTION	04-AUG-1998	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	13-OCT-1998		30-SEP-1998		DAMBROGIOJ
INSPECTION PERFORMED	05-NOV-1998		30-SEP-1998		DAMBROGIOJ
DO RECOMMENDATION	14-DEC-1998			ACCEPTABLE INSPECTION	DAMBROGIOJ
OC RECOMMENDATION	14-DEC-1998			ACCEPTABLE DISTRICT RECOMMENDATION	DAMBROGIOJ

Establishment: [redacted]

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

[redacted]

DMF No: AADA:
Responsibilities: FINISHED DOSAGE MANUFACTURER
Profile: TCT OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	03-AUG-1998				WALSH
SUBMITTED TO DO	03-AUG-1998	PS			DAMBROGIOJ
ASSIGNED INSPECTION	04-AUG-1998	PS			DAMBROGIOJ
INSPECTION SCHEDULED	13-OCT-1998		18-SEP-1998		DAMBROGIOJ
INSPECTION PERFORMED	26-OCT-1998		18-SEP-1998		DAMBROGIOJ
DO RECOMMENDATION	05-FEB-1999			ACCEPTABLE INSPECTION	EGASM
OC RECOMMENDATION	05-FEB-1999			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

[redacted]

APPEARS THIS WAY
ON ORIGINAL

CONSULTATION REQUEST/RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE SENT: January 3, 2000	DUE DATE: January 6, 2000	OPDRA CONSULT #: 99-082

TO (Division):
Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

PRODUCT NAME: **Protonix®** (Pantoprazole Delayed Release Tablets) 40mg NDA #: 20-987	MANUFACTURER: Wyeth Ayerst Laboratories

CASE REPORT NUMBER(S): N/A

SUMMARY:
In response to a November 15, 1999, consult from the Division of Gastro-Intestinal and Coagulation Drug Products (HFD-180), OPDRA conducted a review of the proposed proprietary name "Protonix®" to determine the potential for confusion with approved/unapproved proprietary and generic names.

OPDRA RECOMMENDATION:
OPDRA has no objections to the use of proprietary name "Protonix®".

/S/ 1/3/00
Jerry Phillips
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3246
Fax: (301) 480-8173

/S/ 1/4/00
Peter Honig, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B03
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 12/9/99

NDA#: 20-987

NAME OF DRUG: Protonix®

NDA Holder: Wyeth-Ayerst Laboratories

I. INTRODUCTION

This consult was written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products on November 15, 1999, to review the proposed proprietary drug name, Protonix®, in regard to potential name confusion with existing proprietary/generic drug names.

The Labeling and Nomenclature Committee (LNC) had reviewed this proprietary name on 9/3/98 and concluded that the proposed proprietary name Protonix® was acceptable. This consult was forwarded to OPDRA for final clearance prior to approval of the NDA. The goal date is 2/3/00.

PRODUCT INFORMATION

Protonix® (pantoprazole sodium) is supplied as a delayed-release tablet for oral administration. Each delayed-release tablet contains 45.1 mg of pantoprazole sodium sesquihydrate equivalent to 40 mg pantoprazole.

Protonix® is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration and area under the serum concentration time curve increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.

The absorption of pantoprazole is rapid, with a C_{max} of 2.5 ug/ml that occurs approximately 2.5 hours after single or multiple oral 40 mg doses. Pantoprazole is well absorbed, and is extensively metabolized in the liver through the cytochrome P450 system. Pantoprazole absorption is not affected by concomitant administration of antacids. Administration of pantoprazole with food may delay its absorption up to 2 hours or longer, however, the C_{max} and the extent of pantoprazole absorption

(AUC) are not altered. Thus, pantoprazole may be taken without regard to timing of meals.

Protonix® will be supplied as 40mg delayed-release tablets.

II. RISK ASSESSMENT:

In order to determine the potential for medication errors and to find out the degree of confusion of the proposed proprietary name, Protonix® with other drug names, the medication error staff of OPDRA searched Micromedex online, PDR (1999 Edition), Martindale (30th Edition), American Drug Index (43rd Edition), Drug Facts and Comparison (updated monthly), the Electronic Orange Book, and US Patent and Trademark Office online database. In addition, OPDRA also searched several FDA databases for potential sound-alike and look-alike names to approved/unapproved drug products through DPR, Medline online and LNC database. A focus group was conducted to review all the findings from the searches. In addition, OPDRA conducted studies of written and verbal analysis of the proposed proprietary name employing health practitioners within CDER to evaluate potential errors handwriting and verbal communication of the name. This exercise was conducted to simulate an actual practice setting.

A. STUDY CONDUCTED WITHIN OPDRA

Methodology:

This study involved 90 health professionals consisting of physicians, nurses and pharmacists within CDER to determine the degree of confusion of Protonix® with other drug names due to the similarity in handwriting and verbal pronunciation of the name. OPDRA staff member wrote two outpatient prescriptions and one inpatient order, each consisting of a known drug product and a prescription for Protonix®. These prescriptions were scanned into the computer and a random sample of the written orders were then delivered to the participating health professionals via e-mail. Outpatient prescriptions were sent to 30 participants for review and inpatient orders were also sent to 30 participants. In addition, one pharmacist with an accent recorded the outpatient orders on voice mail. The voice mail messages were then sent to 30 participating health professionals for their review and interpretation. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

Results:

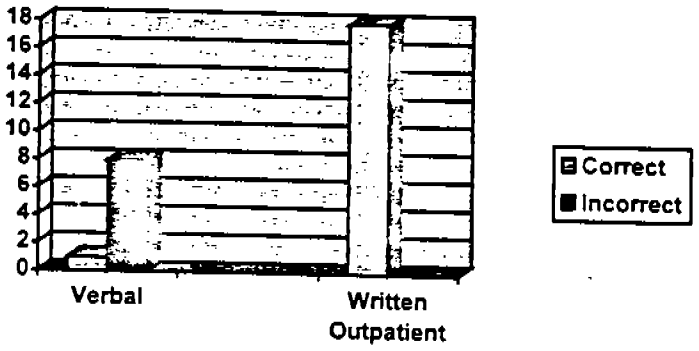
We received responses from 28 participants (out of 90), twenty of which interpreted the name correctly. There was only one correct response for interpretation for inpatient order. Since this response rate was too low, we did not include the inpatient interpretation study in this analysis. Eighteen interpreted

outpatient prescriptions and nine interpreted verbal orders.

Results are summarized in Table 1.

Table 1

Study	# of Sample	# of Responses (%)	Correctly Interpreted	Incorrectly Interpreted
Written Outpatient	30	18 (60%)	18	0
Verbal	30	9 (30%)	1	8



Seventy percent of the participants responded with the correct name Protonix®. All written prescriptions were interpreted correctly. The incorrect verbal responses are as follows:

Protenex
Protonex
Protonex
Protemax
Trotonex
Protonex
Protonex
Protonex

B. FOCUS GROUP STUDY:

The group did not uncover any existing drug names that could cause confusion with Protonix®, and thus pose a significant safety risk.

C. DISCUSSION:

The results of the verbal and written analysis studies show nineteen out of twenty-seven participants interpreted the proprietary name Protonix® correctly. However, there are high scores of correct interpretation for all written prescriptions for this new proposed proprietary name Protonix®. There were eight incorrect verbal responses. Six of which interpreted Protonix® as Protenex, one interpreted Protemax and one interpreted Trotonex. These responses pose little concern since Protonex, Protemax and Trotonex are not proprietary names that are currently marketed. Finally, the studies and searches conducted within OPDRA did not reveal any existing drug names that would render the proprietary name, Protonix®, objectionable.

III. RECOMMENDATIONS

OPDRA has no objections to the use of the proprietary name Protonix®.

Should you have any questions concerning this review, please contact Peter Tam at 301-827-3241

/S/

Peter Tam, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur:

/S/ 1/3/00

Jerry Phillips, RPh.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

C.C.

NDA 20-987
HFD-180; Maria R. Walsh, Project Manager, DGCDP
HFD-180; Lilia Talarico, Division Director, DGCDP
Office Files
HFD-440; Ann Corken, Safety Evaluator, DDREII
HFD-400; Jerry Phillips, Associate Director, OPDRA
HFD-400; Peter Honig, Deputy Director, OPDRA
HFD-002; Murray Lumpkin, Acting Director, OPDRA

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT #	HFD#	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
1043	180	PROTONIX	Pantoprazole Tablets

ATTENTION: MARIA R. WALSH

A. Look-alike/Sound-alike

	Potential for confusion:
PROTROPIN	XXX Low ____ Medium ____ High
PROLIXIN	XXX Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

XXX Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 9/3/98

cc: Orig NDA 20-987
HFD-180 / DIVISION FILE
HFD-180 / M. WALSH
/ H. GALLO-TORRES

REQUEST FOR TRADEMARK REVIEW

Walsh

To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products		**HFD-180**
Attention: Maria R. Walsh, Project Manager	**Phone:** (301) 443-0487	
Date: July 6, 1998		
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product		
Proposed Trademark: Protonix	**NDA/ANDA#** NDA 20-987	
Established name, including dosage form: pantoprazole tablets		
Other trademarks by the same firm for companion products: N/A		
Indications for Use (may be a summary if proposed statement is lengthy): short-term treatment of erosive esophagitis in patients with gastroesophageal reflux disease (GERD).		
Initial Comments from the submitter (concerns, observations, etc.): None		

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original NDA 20-987; HFD-180/division file; HFD-180/M.Walsh; HFD-180/M.Kowblansky

APPEARS THIS WAY
ON ORIGINAL

EXCLUSIVITY SUMMARY FOR NDA # 20-987 SUPPL #_____

Trade Name: Protonix Generic Name: pantoprazole sodium

Applicant Name: Wyeth-Ayerst Laboratories HFD #180

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety? NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /X/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II. #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO." GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

APPEARS THIS WAY
ON ORIGINAL

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

/S/
Signature
Title: RPM

1/19/00
Date

/S/
Signature of Office/
Division Director

1-26-00
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

NDA No. 20-987

PATENT INFORMATION UNDER SECTION 505(b)

PROTONIX™ (pantoprazole sodium) is covered by U.S. Patent 4,758,579 which claims the drug substance. The normal expiration date of said patent is July 19, 2005. An application for extension of said date under the terms of the Drug Price Competition and Patent Term Restoration Act of 1984 will be filed upon approval of the NDA. Patent Information will be updated upon issuance of a certificate of patent term extension. The applicant is the exclusive licensee of this patent. In the opinion of applicant and to the best of applicant's knowledge, there is no other U.S. patent which claims the drug for which applicant has sought approval or which claims the use of the drug for which applicant has sought approval.

WYETH-AYERST LABORATORIES

By: _____
Arthur G. Seifert
Patent Attorney

APPEARS THIS WAY
ON ORIGINAL

Patent/Exclusivity Information

1)	Active ingredient(s)	Pantoprazole Sodium
2)	Strength(s)	40 mg.
3)	Trade Name	PROTONIX™
4)	Dosage Form (Route of Administration)	Tablets, Enteric Coated, Oral
5)	Applicant Firm Name	Wyeth-Ayerst Laboratories
6)	NDA Number	20-987
7)	Approval Date	TBD
8)	Exclusivity - Date first ANDA could be submitted or approved and length of exclusivity period	Pursuant to Section 505(j)(4)(D)(ii) and 505(c)(3)(D)(ii) of the Federal Food, Drug and Cosmetic Act, no ANDA may be submitted prior to 5 years after the date of approval of this NDA.
9)	Applicable patent numbers and expiration date of each	U.S. Patent 4,758,579, Normal Expiration Date: July 19, 2005.

Pantoprazole Sodium
Item 16

NDA No. 20-987

PROTONIX™ (pantoprazole sodium) Enteric-Coated Tablets

NDA No. 20-987

Item 16. Certification Required by Generic Drug Enforcement Act of 1992

The undersigned certifies that Wyeth-Ayerst did not and will not knowingly use in any capacity the services of any person debarred under subsection (a) or (b) [section 306 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with NDA No. 20-987 PROTONIX™ (pantoprazole sodium) Enteric-Coated Tablets.

Signed:
Justin R. Victoria
Vice President, Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

NDA 20-987

FEB 3 2000

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

Dear Dr. DeLorme Sullivan:

Please refer to the meeting between representatives of your firm and FDA on November 29, 1999. The purpose of the meeting was to discuss the Agency's concerns regarding genotoxicity and carcinogenicity as reflected in the draft labeling and the clinical development plan.

A copy of our minutes of that meeting is enclosed. These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you have regarding the meeting outcomes.

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

Sincerely,

/S/ 2/3/00

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

Enclosure

APPEARS THIS WAY
ON ORIGINAL

WASH

Executive CAC
Date of Meeting: October 19, 1999

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Abby Jacobs, Ph.D., HFD-540, Alternate Member
Jasti Choudary, B.V.Sc., Ph.D., HFD-180, Team Leader
Timothy W. Robison, Ph.D., HFD-180, Presenting Reviewer

Author of Minutes: Timothy W. Robison, Ph.D.

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

IND/NDA # 20,987
Drug Name: Pantoprazole
Sponsor Wyeth-Ayerst Research

Dose Selection for p53(+/-) transgenic mouse carcinogenicity study
The sponsor has proposed to conduct a 26-week carcinogenicity with pantoprazole in p53(+/-) transgenic mice at oral doses of 0, 62.5, 125, and 250 mg/kg/day. Further, the sponsor has proposed to include related drug substances, omeprazole and lansoprazole, in this study as comparators, both at oral doses of 150, 360, and 900 mg/kg/day. Dose selection was based a 28-day dose range finding study in which C57BL/6 mice received either pantoprazole, lansoprazole, or omeprazole at doses of 150, 360, or 900 mg/kg/day. The control group received the vehicle denoted as Formulation A. An additional three groups of mice received pantoprazole at oral doses of 150, 350, or 900 mg/kg/day with the drug administered in vehicle denoted as Formulation B; however, there was no corresponding vehicle-control group. All animals that received pantoprazole at 900 mg/kg/day died within 7 days after the start of treatment. One male mouse that received pantoprazole at 360 mg/kg/day (Formulation B) died on day 5 of the study. Renal lesions were observed in mice that received pantoprazole at 360 mg/kg/day (Formulations A and B); however, these lesions were considered of questionable significance. Based upon mortality observed for pantoprazole at 900 mg/kg/day, there was general agreement among committee members that 250 mg/kg/day was a close approximation to the maximum tolerated dose (MTD). Based upon the general lack of findings for lansoprazole and omeprazole in the 4-week dose range finding study, it was difficult to identify MTDs for these two drugs. The majority of committee members agreed that 900 mg/kg/day was the closest approximation possible to the MTDs for both of these two drugs. One committee member disagreed and proposed that MTDs for both of these drugs were ≤ 500 mg/kg/day. The mid and low doses suggested by the committee for both lansoprazole and omeprazole were 360 and 125 mg/kg/day, respectively.

Executive CAC Recommendations and Conclusions:

1. For the 26-week carcinogencity study with p53(+/-) transgenic mice, the committee recommended doses of pantoprazole, lansoprazole, and omeprazole as follows:
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. In the protocol for the carcinogenicity study, all gross lesions and tissues from all animals in the vehicle-control, positive control, and all pantoprazole treatment groups will be processed and subjected to microscopic examination. For lansoprazole and omeprazole treatment groups, gross lesions and all tissues from the high dose groups animals and animals that died or were sacrificed in a moribund condition during the study period will be processed and subjected to microscopic examination. Since the sponsor plans histological evaluation of tissues from only the high dose lansoprazole and omeprazole treatment groups, they will also need to conduct histopathologic examination of the corresponding mid and low dose groups under any of the following circumstances:
(a) for any macroscopic findings in the low and mid dose groups for a given tissue, they will need to look at that tissue for all of the 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, they will also need to look at the next lower dose group;
(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) they should look at all relevant tissues for that dose level and the next lower dose level; and
(d) for an excessive decrease in body weight or survival in the examined dose group, they should examine lower dose groups.
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.

3. In the case of positive results with lansoprazole and/or omeprazole in the 26-week carcinogenicity study with p53(+/-) transgenic mice, the sponsor should provide respective drug composition(s) and impurity profile(s).

/S/ 10/20/99
Joseph DeGeorge, Ph.D.
Chair, Executive CAC
cc:\
/Division File, HFD-180
/Dr. Choudary, HFD-180
/Dr. Robison, HFD-180
/Maria Walsh, HFD-180
/ASeifried, HFD-024

Memorandum 6/28/99

To Dr. Florence Houn,
Ms. Bronwyn Collier
Dr. Jasti Choudary

It is my understanding that in light of the conclusions of the CAC, the Office review of the package, and commitment by the sponsor to conduct additional studies phase 4, that NDA 20987 will be approvable for short treatment of GERD

In light of this I have the following comments on the package:

1) The pharmacology and toxicology sections of the package are adequate with the commitment to conduct the additional studies.

2) The evaluation of the tumor findings by NCTR is essentially complete with the report of _____ dated June 24, 1999. The outstanding assessment of animal 5100, given _____ preliminary report, is unlikely to have any regulatory impact. The tumor assessed for this animal and designated as a "mixed tumor, malignant..." is adequate for our assessment of potential risk which will not be further assisted by greater phenotypic discrimination.

3) I generally agree with Dr. Choudary's memorandum dated June 25, 1999.

4) I recommend the following revisions of his recommendations for labeling in the carcinogenicity section of the label
a) Use of approximations of fold exposure, thus 0.1-40
b) Deletion of "_____"
c) Deletion of _____
d) Addition of "about 10 and 40 times the recommended human dose on a body surface area basis" after the first time "50 and 200 mg/kg/day" is mentioned
e) Revision of the paragraph regarding sporadic tumors being observed to the effect that "x, y and z tumors were observed in other chronic toxicity studies in SD rats" without reference to the specific duration of treatment. Otherwise the specific tumors found in each of the studies should be listed separately.

4) Deletion of the

[redacted]

5) The pregnancy section of the label should be similarly revised regarding reporting of doses and fold of exposure.

6) Additional comments and revisions may be necessary pending the sponsor's response to proposed labeling.

This memorandum is to serve in place of the Action letter Routing Record regarding Pharmacology and Toxicology.

Joseph DeGeorge

APPEARS THIS WAY
ON ORIGINAL

9 PAGE(S) REDACTED

Draft

MEMORANDUM

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

PID# 99372 DEC - 7 1999

DATE:

FROM: Ann Corken, R.Ph., M.P.H., Safety Evaluator
Division of Drug Risk Evaluation II (DDRE II)

THROUGH: Evelyn M. Rodriguez, M.D., M.P.H., Director
DDRE II/ HFD-440

12/07/99

TO: Lilia Talarico, M.D., Division Director
Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: OPDRA Postmarketing Safety Review:
Pantoprazole (Protonix) and allergic reactions and/or death

EXECUTIVE SUMMARY:

Gastrointestinal and Coagulation Drug Products (HFD-180) requested from FDA's Adverse Event Reporting System (AERS) database reports of allergic reactions associated with pantoprazole, especially anaphylaxis or anaphylactoid reactions with severe CNS manifestations (e.g., coma, lethargy, decreased level of consciousness) and/or death. Based on the information from the AERS database, the WHO database, and MEDLINE, it appears that few cases of serious allergic reactions and/or death have been associated with pantoprazole use.

BACKGROUND:

This memorandum is in response to a consult received from Gastrointestinal and Coagulation Drug Products (HFD-180) to review FDA's Adverse Event Reporting System (AERS) database for reports of allergic reactions associated with pantoprazole, especially anaphylaxis or anaphylactoid reactions with severe CNS manifestations (e.g., coma, lethargy, decreased level of consciousness) and/or death.

Pantoprazole (Protonix) is an oral proton pump inhibitor and is manufactured by Wyeth-Ayerst. It is available worldwide, but has not been approved for use in the U.S. at this time. HFD-180 is currently considering the drug for approval; they have received

SELECTION OF CASES:

AERS CASES

On November 4, 1999, a search was performed in AERS using pantoprazole as suspect drug. The search produced a total of 6 unduplicated reports, none of which were associated with allergic reactions. Two patients died while receiving pantoprazole; however, one patient died of underlying renal failure and the other patient died from shock and multiple organ system failure resulting from toxic epidermal necrolysis which was thought to be induced by any of four medications that the patient was taking (i.e., amphotericin B, famotidine, furosemide, pantoprazole).

WHO DATA

A report (by organ system) of adverse reactions to pantoprazole from the WHO database is attached for your review. As you can see from the summaries found on pages 9 to 14 of the document (note that there are separate summaries for pantoprazole and pantoprazole sodium), there were 4 cases of anaphylactoid reaction/anaphylactoid shock, 3 cases of "allergic reaction," and 2 cases of sudden death out of a total of 850 adverse reactions reported. Several symptoms listed in the document could be a result of an allergic reaction to pantoprazole (e.g., bronchospasm, rash, urticaria). The WHO document contains 3 reports of coma, but it cannot be determined if the coma resulted from an allergic reaction to pantoprazole, since a listing of individual cases was not provided.

LITERATURE

As of November 10, 1999, a MEDLINE search of the published English-language literature using the term pantoprazole produced no individual case reports of allergic reaction and/or death.

DISCUSSION/CONCLUSION:

This document describes the results of a search of the AERS database, the WHO database, and the medical literature for reports of allergic reactions and/or death associated with the use of pantoprazole. Based on the information from these three sources, it appears that there have been few cases of serious allergic reactions and/or death associated with pantoprazole use

[redacted]. Since pantoprazole has not been approved in the U.S., numerous reports in AERS would not be expected. We will continue to monitor pantoprazole reports for additional evidence of serious allergic reactions and/or death and update you if more information becomes available.

/S/

Ann Corken, R.Ph., M.P.H.

Concur:

/S/

Toni Piazza-Hepp, Pharm.D., Team Leader