

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-020

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-020

SUPPL # N/A

HFD # 180

Trade Name Protonix For Delayed-Release Oral Suspension

Generic Name pantoprazole sodium

Applicant Name Wyeth Pharmaceuticals, Inc.

Approval Date, If Known November 14, 2007

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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 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.

The next three paragraphs are taken from the November 7, 2007 Clinical Pharmacology review of this NDA:

"The key element of the clinical development program supporting this NDA was the pharmacodynamic comparability study designed to bridge the proposed granule formulation to the marketed tablet formulation. Therefore, no efficacy trials were conducted with the pantoprazole sodium delayed-release granules. The applicant did not conduct a bioequivalence study between the to-be-marketed granule formulation and the marketed tablet formulation either.

The clinical development program consisted of 5 studies. The 2 pivotal clinical studies (3001B1-332-US and 3001B1-116-US) were conducted using the to-be-marketed pantoprazole sodium delayed-release granules formulation. Study 3001B1-332-US was performed to demonstrate the pharmacodynamic comparability of the to-be-marketed granules formulation to the marketed tablet formulation. Study 3001B1-116-US was carried out to establish bioequivalence among the 3 proposed methods for administration of the granules.

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In their objective to Study 3001B1-332-US, the applicant stated that the study was intended to demonstrate "pharmacodynamic comparability". Although the study is not strictly a comparative bioequivalence study, it could be considered a confirmatory study, and not a clinical study used to establish efficacy and safety of the new dosage form. According to the objectives of the study, the intent was not to establish efficacy for the new dosage form, but to show pharmacodynamic (or therapeutic) comparability between the new dosage form and the approved dosage form. The data was presented as demonstrating pharmacodynamic comparability and not establishing efficacy.

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:

N/A

d) Did the applicant request exclusivity? YES NO

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

Three

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

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 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

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

NDA# 20-987 Protonix (pantoprazole sodium) Delayed-Release Tablets

NDA# 20-988 Protonix I.V. (pantoprazole sodium) for Injection

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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

(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"):

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 ! NO
Explain: ! Explain:

Investigation #2 !
!
YES ! NO
Explain: ! 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:

Name of person completing form: Brian Strongin, R.Ph., M.B.A.
Title: Chief, Project Management Staff, Division of Gastroenterology Products
Date: November 14, 2007

Name of Office/Division Director signing form: Joyce Korvick, M.D, M.P.H.
Title: Deputy Director, Division of Gastroenterology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Joyce Korvick
12/18/2007 10:19:16 AM

NDA 22-020
(3/12/08
Submission)

Pantoprazole Sodium
Delayed-Release

1.9 Pediatric Administrative Information
1.9.2 Request Deferral Pediatric Studies

b(4)

1.0 REQUEST FOR DEFERRAL OF PEDIATRIC STUDIES

As discussed in 21 CFR 314.55, each new application for a new indication or dosing regimen shall contain data that are adequate to assess the safety and efficacy, and to support the dosing of the drug for the claimed indication in all relevant pediatric subpopulations.

The current application does not include data in a population of pediatric patients. Children ≤ 18 years of age were excluded from participation in these studies.

At the 23 June 2005 pre-NDA teleconference with the FDA, Wyeth requested deferral of the PREA requirements. FDA concurred that the PREA date for this NDA would correspond to the due date of 31 December 2008 for the Written Request (WR) for Pediatric studies.

Accordingly, as per 21 CFR 314.55(b), Wyeth Research is formally requesting a deferral for the submission of data for the use of Pantoprazole Sodium Delayed-Release in pediatric patients.

b(4)

Appears This Way
On Original

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 22-020

Supplement Type (e.g. SE5):

Supplement Number:

Stamp Date: May 15, 2006

Action Date: March 15, 2007

HFD 180

Trade and generic names/dosage form: Protonix Delayed Release 40mg

b(4)

Applicant: Wyeth Pharmaceuticals, Inc.

Therapeutic Class: 3

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 3

Indication #1: Short-term Treatment of Erosive Esophagitis Associated with Gastroesophageal Reflux Disease (GERD).

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 1 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): 12/31/2008 per Written Request December 31, 2001 (NDA 20-987)

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Thomas Moreno
Regulatory Project Manager

cc: NDA 22-020
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Maintenance of Healing of Erosive Esophagitis.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 1 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): 12/31/2008 per Written Request December 31, 2001 (NDA 20-987)

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}
Thomas Moreno
Regulatory Project Manager

cc: NDA 22-020
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

Indication #3: Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome.

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: This indication waived per agency letter dated April 2, 2001

b(4)

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. 1 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): 12/31/2008

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Thomas Moreno
Regulatory Project Manager

cc: NDA 22-020
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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this page is the manifestation of the electronic signature.**

/s/

Hugo Gallo Torres
9/13/2006 05:13:54 PM

**CERTIFICATION: FINANCIAL INTERESTS AND
ARRANGEMENTS OF CLINICAL INVESTIGATORS**

TO BE COMPLETED BY APPLICANT

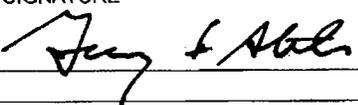
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	Pantoprazole	Study 332-US

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Dr. Gary L. Stiles Mr. Gary Gallagher		TITLE Executive Vice President & Chief Medical Officer Vice President- R&D Finance	
FIRM / ORGANIZATION Wyeth Research			
SIGNATURE 		DATE 2/13/06 2/8/06	

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 68,011

Wyeth Pharmaceuticals
Attention: Henrietta Ukwu, M.D., F.A.C.P.
Vice President, Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Ukwu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505 (b)(2) of the Federal Food, Drug, and Cosmetic Act for Pantoprazole Sodium Delayed-Release

b(4)

We also refer to the teleconference between representatives of your firm and the FDA on June 23, 2005. The purpose of the meeting was to discuss the content of the planned NDA.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Mary Lewis, Regulatory Project Manager, at (301) 827-7475.

Sincerely,

Suresh Doddapaneni, Ph.D.
Pharmacokinetic Team Leader
Office of Clinical Pharmacology and
Biopharmaceutics
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

Strongin, Brian K

From: Strongin, Brian K
Sent: Wednesday, November 14, 2007 4:50 PM
To: CDER-APPROVALS
Cc: Strongin, Brian K; Korvick, Joyce A
Subject: Approval: NDA 22-020 Protonix (pantoprazole sodium) For Delayed-Release Oral Suspension
Attachments: Protonix Approval Letter.pdf

Today, November 14, 2007, the Division of Gastroenterology Products approved the following new drug application:

Applicant: Wyeth Pharmaceuticals, Inc.

NDA: 22-020

Established Name: pantoprazole sodium

Proprietary Name: Protonix For Delayed-Release Oral Suspension

Indications:

Short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD)

Maintenance of healing of erosive esophagitis

Pathological hypersecretory conditions including Zollinger-Ellison syndrome

Route of Administration: Oral

Dosage (adult):

Short-term treatment of erosive esophagitis associated with gastroesophageal reflux disease (GERD)- 40 mg daily for eight weeks, an additional eight week course may be necessary

Maintenance of healing of erosive esophagitis - 40 mg daily

Pathological hypersecretory conditions including Zollinger-Ellison syndrome - starting dose is 40 mg twice daily, dosages up to 240mg daily have been administered

Date of Approval: November 14, 2007

Enclosed is the approval letter with the agreed upon final package insert.



Protonix Approval
Letter.pdf (...)



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: November 9, 2007

To: Joanne Palmisano, M.D.	From: Brian Strongin
Company: Wyeth Research	Division of Gastroenterology Products
Fax number:	Fax number (301) 796-9905
Phone number: (484) 865-9922	Phone number: (301) 796-1008
Subject: NDA 22-020 Protonix Delayed-Release for Oral Suspension: Language Regarding Atazanavir Drug – Drug Interaction	

Total no. of pages including cover: 2

Comments:

Please our proposed language for the Atazanavir Drug-Drug Interaction. Thanks.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-7310. Thank you.

Please see the following proposed language for the Atazanavir Drug – Drug Interaction discussed in our labeling meeting today:

PRECAUTIONS

Drug Interactions

Concomitant use of atazanavir and proton pump inhibitors is not recommended.

Coadministration of atazanavir with proton pump inhibitors is expected to substantially decrease atazanavir plasma concentrations and thereby reduce its therapeutic effect.

The above recommendations are based on:

1. EMEA Public Statement, December 21, 2004. "Important new pharmacokinetic data demonstrating that REYATAZ (atazanavir sulfate) combined with NORVIR (ritonavir) and omeprazole should not be co-administered."
2. 2007 Product Labeling for REYATAZ (atazanavir sulfate).

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this page is the manifestation of the electronic signature.**

/s/

Brian Strongin
11/13/2007 09:38:47 AM
CSO



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEIII

FACSIMILE TRANSMITTAL SHEET

DATE: October 19, 2007

To: Joanne Palmisano, M.D.	From: Brian Strongin, R.Ph., M.B.A.
Company: Wyeth Pharmaceuticals	Division of Gastroenterology Products
Fax number: (484) 865-9197	Fax number:
Phone number: (484) 865-9922	Phone number: (301) 796-2120
Subject: NDA 22-020 Protonix Delayed-Release <input checked="" type="checkbox"/> <input type="checkbox"/> Biopharm Information Request	

Total no. of pages including cover: 3

Comments:

Please respond to the attached information request ASAP. Please e-mail the response to me followed by submission of hardcopy. Thanks.

Document to be mailed: YES NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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For NDA 22-020: Please provide the following information ASAP

Please provide a data listing of the volume of apple juice that was actually mixed with the Protonix Delayed-Release and administered to each subject for the "oral administration in apple juice" and the "nasogastric tube administration" in study 3001-B1-116US entitled "An open-label, randomized, 3-period, crossover, bioequivalence study of the to-be-marketed formulation of pantoprazole sodium enteric coated spheroids administered in 3 dose regimens to healthy subjects".

b(4)

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/s/

Brian Strongin
10/19/2007 10:42:49 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-020

Wyeth Pharmaceuticals
Attention: Joanne Palmisano, M.D.
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Palmisano:

We acknowledge receipt on August 2, 2007 of your August 1, 2007 resubmission to your new drug application for Protonix® (pantoprazole sodium) Delayed Release

b(4)

We consider this a complete, class 1 response to our March 15, 2007 action letter. Therefore, the user fee goal date is October 2, 2007.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled this requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application.

If you have any questions, call me at (301) 796-1008.

Sincerely,

{See appended electronic signature page}

Brian Strongin, R.Ph., M.B.A.
Chief, Project Management Staff
Division of Gastroenterology Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Brian Strongin
9/28/2007 08:36:17 AM

MEMORANDUM

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

DATE: December 22, 2006

TO: Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products

FROM: Michael F. Skelly, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDA 22-020, Protonix Delayed Release [] (pantoprazole sodium), Sponsored by Wyeth Pharmaceutical Inc. **b(4)**

At the request of DMEP, the Division of Scientific Investigations audited clinical and analytical portions of the following bioequivalence study.

Study# 3001B1-332-US: A Randomized, 2-Period, Crossover, Pharmacodynamic Comparability Study Comparing a Pantoprazole Sodium Spheroid Formulation to the Currently Marketed Tablet Formulation in Subjects with GERD and a History of Erosive Esophagitis

Following the inspection at [] **b(4)**
[] no Form FDA 483 was issued. Following the inspection []
[] Form FDA 483 was issued. The objectionable observations and our evaluation are provided below: []

b(4)

1. Failure to demonstrate the performance of the assay for titratable acid in gastric aspirates
 - A. Individual runs were not conducted with calibrators and quality control samples at multiple concentrations. Runs were accepted on the basis of a single "titration check" sample, consisting of 0.1 N HCl in water.
 - B. There was no demonstration that the assay was not affected by shipment of sample tubes with dry ice, or the presence of particulates, salts, and other normal constituents of gastric fluids. Some samples were shipped frozen from the clinical sites in dry ice, in violation of the protocol. Samples were not centrifuged or filtered to remove particulates.
 - C. There was no evaluation of recovery of HCl added to samples of gastric aspirates.
 - D. There was no measurement of, or adjustment for, titratable acid in reagent blanks.
 - E. The assay did not confirm increased acid secretion in a "maximal acid output" validation sample relative to its "basal acid output" validation sample. The single samples were used for evaluating storage stability. The stimulation for the maximal acid output sample was said to be "cephalic-vagal" stimulation, without a further definition available from the outside collection site. Although it was recognized at the time that the stimulation failed to increase acid output, and possibly caused samples to be diluted with saliva, the stability experiment was not repeated.

b(4)

Thus, the assay method for the pharmacodynamic endpoint measurement was not calibrated in each run, and there were insufficient quality control samples during the study either to demonstrate accuracy and precision or to justify run acceptance. The "titration check" sample and a single sample each of gastric aspirate for "basal acid output" and "maximal acid output" were not representative of the study samples, and do not suffice to validate the assay.

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2. Failure to retain records of laboratory operations performed for validation and testing. Only observations, intermediate calculations, and reported results were retained.

There were almost no details of how personnel actually did the validation and study testing.

3. Two runs were accepted although the "titration check" results were outside the specified acceptance limits of true concentration). Examples: two runs on 7/15/2005

b(4)

Personnel did not reject these runs, and reassay the samples, as required by the established procedure.

4. The analyst did not sign and date all original data entries on the day of acquisition. Example: One set of initials for work dated 8/25/05 and 8/26/05

In the example, the data entries on each day are not attributable to an individual analyst.

5. Only the first page of autotitrator displays was printed. The second page, with data for titration to the pH 7.0 endpoint, was not printed. The acid output calculations relied solely on titrations to pH 7.0.

The page containing the crucial data was not printed. Only a handwritten entry documented the instrumental result.

DSI reviewed response to the observations; the response does not contradict the observations.

b(4)

Conclusions:

DSI recommends that the analytical data for the pharmacodynamic endpoint in study 3001B1-332-US are **not** acceptable for review, because of insufficient method validation, calibration, quality control, and documentation.

After you have reviewed this transmittal memo, please append it to the original NDA submission.

Michael F. Skelly, Ph.D.
Pharmacologist

b(4)

Final Classifications:

NAI - []

VAI - []

b(4)

Recommendation: Pharmacodynamic data from study 3001B1-332-US are **not** acceptable for review.

- cc:
- DMEP/Moreno/NDA 22-020/
- HFA-224
- HFD-45/RF
- HFD-48/Himaya
- HFD-48/CF
- HFR-PA250/VanLeeuwen
- HFD-SE1535/Frazier
- OCP/DCP3/Adebowale
- Drafted: MFS 12/22/06
- DSI: 5709; O:\BE\EIRCover\22020wye.pan.doc
- FACTS: 755051

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/s/

Michael Skelly
12/22/2006 02:05:13 PM
PHARMACOLOGIST

The paper copy of this document was signed by
Drs. CT Viswanathan and MF Skelly on 12/22/06.

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-020 Supplement # Efficacy Supplement Type SE-

Trade Name: Protonix Delayed Release
Established Name: pantoprazole sodium
Strengths: 40 mg

b(4)

Applicant: Wyeth Pharmaceuticals
Agent for Applicant: Jethro Ekuta, D.V.M., Ph.D., Director, Global Regulatory Affairs

Date of Application: May 12, 2006
Date of Receipt: May 15, 2006
Date clock started after UN: N/A
Date of Filing Meeting: July 6, 2006
Filing Date: July 14, 2006
Action Goal Date (optional): User Fee Goal Date: March 15, 2007

Indication(s) requested: Short-term treatment of patients with gastroesophageal reflux disease (GERD) and a history of Erosive Esophagitis; maintenance of healing of Erosive Esophagitis; and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S P
Resubmission after withdrawal? N/A Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will

Best Possible Copy

for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO
If yes, explain:
- Does another drug have orphan drug exclusivity for the same indication? YES NO
- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES NO
- Does the submission contain an accurate comprehensive index? YES NO
- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:
- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format

Additional comments: In Archival jacket was the cover letter and form FDA 356h.

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A YES NO
- Is it an electronic CTD (eCTD)? N/A YES NO
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: Forms signed and sent electronically were: Prescription Drug User Fee Coversheet; Debarment Certification; Patent Info. Form 3542a; and Certification: Financial Interests form FDA 3454. I was unable to locate the signed Field Copy Certification sheet, and will request sponsor to send this, or inform me where it is located in the original submission. (MML 8/28/06)

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, 3 Years NO

NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . ."

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
FORM 3454 WAS ENCLOSED; FORM 3455 WAS NOT ENCLOSED. MML 8/4/06

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO X
Field Copy Certification to be requested from sponsor. 8/28/06 MMLewis **N/A** *electronic sub.*
- PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered. YES.

- List referenced IND numbers: 68,011; and NDA 20-987; 20-988. b(4)

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) T-con 6/23/05 NO
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES X NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES X NO
- Risk Management Plan consulted to ODS/IO? N/A X YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A X YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A X YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? N/A NO
YES
- Establishment Evaluation Request (EER) submitted to DMPQ? YES X NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

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ATTACHMENT

MEMO OF FILING MEETING

DATE: July 6, 2006

NDA #: 22-020

Drug Name: Protonix (pantoprazole sodium) Delayed Release

b(4)

BACKGROUND: This application is organized using the electronic Common Technical Document (eCTD) format and was submitted as a 505(b)(1) application with half fee payment based on bioavailability/bioequivalence data only. Wyeth Pharmaceuticals is the sponsor for NDA 20-987 Protonix (pantoprazole sodium) Delayed-Release Tablets, 20 mg and 40 mg tablets, approved on February 2, 2000. NDA 20-987 is approved for: short-term treatment of Erosive Esophagitis associated with Gastroesophageal Reflux Disease (GERD); maintenance of healing of erosive esophagitis; and pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Wyeth Pharmaceuticals is also the sponsor of NDA 20-988 for Protonix I.V. (pantoprazole sodium) for injection, 40 mg, approved on March 22, 2001. NDA 20-988 is approved for: gastroesophageal reflux disease associated with a history of erosive esophagitis; and pathological hypersecretion associated with Zollinger-Ellison Syndrome. (Provide a brief background of the drug, e.g., it is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

Joyce Korvick, M.D., Deputy Division Director, Division of Gastroenterology Products
Hugo Gallo-Torres, M.D., Medical Team Leader
Ann Marie Trentacosti, M.D., Medical Reviewer
Jasti Choudary, Ph.D., Supervisory Pharmacologist
Stella Grosser, Ph.D., Biometrics Team Leader
Wen-Jen Chen, Ph.D., Biometrics Reviewer
Marie Kowblansky, Ph.D., Chemistry Team Leader
Zhengfang Ge, Ph.D., Chemistry Reviewer
Suliman Al-Fayoumi, Ph.D., Biopharmaceutics Reviewer
Melissa Furness, Regulatory Health Project Manager
Mary M. Lewis, Regulatory Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:

Reviewer

Ann Marie Trentacosti
Hugo Gallo-Torres
Wen-Jen Chen
Sushanta Chakder
N/A
Zhengfang Ge

Suliman Al-Fayoumi
N/A

Microbiology, clinical (for antimicrobial products only): N/A
 DSI: C.T.Viswanathan
 Regulatory Project Management: Mary M. Lewis
 Other Consults:
 DMETS
 DDMAC

Per reviewers, are all parts in English or English translation? YES X NO
 If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed? YES NO X
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A YES NO X

CLINICAL MICROBIOLOGY N/A X FILE REFUSE TO FILE

STATISTICS N/A X FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE X REFUSE TO FILE

- Biopharm. inspection needed? YES X NO

PHARMACOLOGY N/A FILE X REFUSE TO FILE

- GLP inspection needed? YES NO X

CHEMISTRY FILE X REFUSE TO FILE

- Establishment(s) ready for inspection? YES X NO
- Microbiology YES NO X

ELECTRONIC SUBMISSION: Yes, eCTD.
 Any comments: No.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- X No filing issues have been identified.

Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- 3.X Convey document no filing issues to applicant by Day 74.

Mary M. Lewis 7/24/06
Regulatory Project Manager, HFD-180

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/s/

Mary Lewis
8/28/2006 01:26:16 PM
CSO

Mary Lewis
8/28/2006 01:29:29 PM
CSO

Lewis, Mary

From: Jethro Ekuta [EKUTAJ@wyeth.com]
Sent: Monday, August 28, 2006 2:31 PM
To: Lewis, Mary
Cc: Moreno, Thomas
Subject: Re: NDA 22-020; Protonix Delayed Release Field Copy Certification **b(4)**
Importance: High
Attachments: emfinfo.txt

—Brim Strongin approval 8/28/06
Dear Mary,

We did not include a Field Copy Certification with the NDA (No. 22-020) submission dated May 12, 2006. In the cover letter for the referenced submission, we stated the following rationale for not including a Field Copy Certification:

"21 CFR 314.50(d)(1)(v) requires that applicants include in the NDA a statement certifying that the field copy of the application be provided to the applicant's home FDA District Office. This application is being submitted entirely in electronic Common Technical Document (eCTD) format, and hence, an individual field copy is not being submitted. Although a field copy and accompanying certification are not included in this application, a copy of the cover letter and the 356h form will be submitted to the FDA District Office at Philadelphia, PA, as required under 21 CFR 314.50(I)(3)."

We also based our decision on the FDA Guidance for Industry: *Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions using eCTD Specifications*, issued in October, 2005, which states the following (please refer to Page 6, Section II, Item K):

"K. The FDA District Office Copy

FDA District offices have access to documents submitted in electronic format. Therefore, when sending submissions in electronic format, you need not provide any documentation to the FDA Office of Regulatory Affairs District Office."

Please contact me if you have further questions or if I can be of further assistance to you during the ongoing review our application.

Jethro Ekuta, D.V.M., Ph.D.
Director II
Global Regulatory Affairs
Wyeth Research
500 Arcola Road
Collegeville, PA 19426
Phone: (484) 865-7408
Fax: (484) 865-9197
E-mail: ekutaj@wyeth.com

b(4)

>>> "Lewis, Mary" <Mary.1.Lewis@fda.hhs.gov> 8/28/2006 1:32:42 PM >>>

Hi:

I am unable to locate a signed "Field Copy Certification" in the original electronic submission of May 12, 2006. Would you please send me a signed copy through our document room at Ammendale Road; or inform me where it can be located in the electronic submission.

Thank you.

Mary

Mary M. Lewis, RN, BSN
Regulatory Health Project Manager
Division of Gastroenterology Products
Center for Drug Evaluation and Research
Phone: 301-796-0941
Fax: 301-796-9905

Pls. note new email address:
Mary.1.Lewis@fda.hhs.gov

"MMS <wyeth.com>" made the following annotations on 08/28/2006 02:31:04 PM

*** Notice of Confidentiality ***

This electronic message is intended only for the individual or entity to which it is addressed and may contain information that is confidential and protected by law. If you are not the intended recipient of this e-mail, you are cautioned that use of its contents in any way is strictly prohibited and may be unlawful. No confidentiality or privilege is waived by errant transmission. If you have received this communication in error, please notify the sender immediately by e-mail and return the original message by secure e-mail to the sender or to postmaster@wyeth.com. If you do not have access to secure email please delete the errant email and notify the sender. We will reimburse you for any cost you incur in notifying us of the errant e-mail. Thank you for your cooperation.

=====

Please find below our responses to the questions submitted in your May 20, 2005 Meeting Background Package. Our responses are in **bold**.

IND 68,011

Teleconference June 23, 2005

Questions 1 through 4: Quality

1. When compared to the marketed PROTONIX Delayed-Release Tablets, 40 mg, the spheroid formulation contains three additional excipients, namely Microcrystalline Cellulose, Polysorbate 80 and Talc. All three excipients are commonly used in approved solid oral dosage forms, and are present at levels well below the levels listed in the FDA Inactive Ingredient Guide. Since all three ingredients are used in approved products, does the FDA concur that no additional non-clinical studies are necessary to support the approval of the spheroid formulation?

FDA Response:

Yes. However, the stability of the spheroid formulation in the delivery vehicles (e.g., applesauce, water, apple juice, etc.) should be demonstrated.

2. Does the FDA concur with Wyeth's proposal to update the NDA, during review, with stability data from without affecting the review clock? b(4)

FDA Response:

You may update your stability data no later than three months prior to the PDUFA goal date. Any stability data submitted later than that will either extend the review clock or will not be considered in establishing expiration dating.

3. Since the stability data generated in three registration lots is representative of the stability in child-resistant does the FDA concur with Wyeth's proposal to launch the spheroid product filled in the child-resistant b(4)

FDA Response:

The suitability of child-resistant packaging will be determined as part of the NDA review. A major factor that will be considered is the stability of the product in the proposed packaging. You will also need to conduct stability studies on the bulk-packaged delayed release spheroids, to establish a maximum holding time before which the spheroids must be used for product manufacture. These studies should include an evaluation of the coating.

Discussion Points:

FDA asked the sponsor if the package configuration is identical for the
 the sponsor stated "it is identical".

b(4)

4. Based on the stability proposal, along with interim supporting stability data presented in this briefing package, does the FDA concur with approving the spheroids drug product with an 18-month shelf life based on satisfactory stability data at room temperature of up to 6 months in the registration stability package configuration, and 12-months in Altana spheroids in capsules?

FDA Response:

From the above question it appears that you plan to file your NDA with no stability data and to submit six months of stability data while the NDA is under review. You must submit at least six months of stability data at the time of filing and update your data while the NDA is under review. Since the stability of PPI's has been observed to be quite formulation dependent, we will need a minimum of twelve months of stability data to consider an eighteen month expiry. The 12-month stability data for the delayed release spheroids in capsules will not be considered in determining expiration dating for your product.

Discussion Points:

The sponsor stated they would submit six months of stability data. The FDA responded: and another 6 months stability data during the review must be filed three months before the PDUFA date.

Question 5: Nonclinical

5. To support the IND filing for the spheroid formulation, Wyeth performed a bioequivalence study in dogs comparing the spheroid formulation to the tablet formulation. As there were no meaningful differences in exposure between the two formulations, no additional nonclinical studies for the spheroid formulation were conducted. For the spheroid NDA, reference will be made to the approved NDA 20-987 for PROTONIX® (pantoprazole sodium) Delayed-Release Tablets. Does the FDA concur?

FDA Response:

Yes.

Question 6: Clinical/Statistical

6. In the February 2, 2005 submission (IND 68,011, Serial No. 036) of Protocol 3001A1-332-US Wyeth added, in the eventuality that the spheroids are not equivalent to the tablets in this protocol, another statistical comparison based on a one-sided test (α level = 0.025) which will test that the spheroids are not less effective than the tablets in suppressing maximal acid output (MAO). This approach was used in Protocol 3001K1-309-US (GMR-32141 submitted in the July 20, 1988 NDA 20-988, section 8.4.1.1.1, Vol.1.160. p.88). The results of Protocol 3001K1-309-US demonstrated the therapeutic comparability of the intravenous and tablet formulations and thus supported the approval of PROTONIX® I.V. (pantoprazole sodium) for Injection.

FDA Response:

If it is not possible to establish PD equivalence due to technical limitations of the PD analysis, then establishing therapeutic comparability using a one-sided t-test or signed rank test is not an acceptable approach.

Regarding the to-be-marketed spheroid formulation, clarify if food effect information is available on it, and if it was utilized in study 3001B1-332-US.

Discussion Points:

As the discussion did not result in meaningful outcome, the sponsor indicated that, a clarified proposal of the statistical plan for study 3001B1-332-US will be sent later.

Question 7: PREA Requirements

7. Wyeth is currently conducting a clinical program with pantoprazole sodium in pediatric subjects, 1 month to 4 years of age, with a clinical spheroid formulation in response to the Written Request, issued on December 31, 2001. This program includes the following studies:
- Pharmacokinetics, pharmacodynamics, and safety study of pantoprazole spheroids in suspension in infants 1 month through 11 months of age with GERD (Study 3 of Written Request; Protocol 3001B1-333-US,)
 - Safety and efficacy study of pantoprazole spheroids in suspension in infants 1 month through 11 months of age with GERD (Study 4 of Written Request; Protocol 3001B1-329-US),

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b(4)

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As the product will be ready for approval in adults before studies in pediatric patients are complete, Wyeth requests that the pediatric studies required by the Pediatric Research Equity Act (PREA) for the planned NDA. Does FDA agree?

b(4)

FDA Response:

No. As you know, the WR for the PPI drug class has required extensive input from multiple sponsors, outside consultants, and office and divisions within the FDA. In addition, the information determined to be needed to ensure the safe and effective use in children had required input from multiple experts that have provided feedback regarding the logistical conduct of these studies. We feel that the December 31, 2008 date is a reasonable and appropriate due date. The intent of PREA and BPCA is to generate important information for the safe and effective use of drugs in children. The goal of the current due date for submission of these data is to obtain this information in a prompt and reasonable timeframe. The date that exclusivity or a patent might expire does not generally impact this decision. In addition, we do not feel that this due date is unreasonable as other PPIs are already labeled for children ages 1 to 17. Thus, we request that you make every effort to meet the due date of December 31, 2008. We look forward to receiving and reviewing this information. Please note that submitting your data prior to expiry of applicable patents or exclusivity will warrant granting the exclusivity provided the terms of the WR are met. Given your concerns, we request that you let us know if you intend to conduct the studies detailed in the WR.

Questions 8 and 9: Administrative Information and Prescribing Information

8. Upon successful completion of the ongoing development program, Wyeth intends to update the PROTONIX Delayed-Release Tablets package insert to incorporate information on the spheroid formulation in the following sections:

DESCRIPTION
CLINICAL PHARMACOLOGY Pharmacokinetics
CLINICAL PHARMACOLOGY Pharmacodynamics
INDICATIONS AND USAGE
PRECAUTIONS Information for Patients
ADVERSE REACTIONS
DOSAGE AND ADMINISTRATION
HOW SUPPLIED

Does FDA agree with the proposed labeling strategy for the planned NDA?

FDA Response:

This strategy appears acceptable, but our final answer will be dependent on the results of your data and will be discussed during labeling negotiations.

9. Wyeth intends to provide the planned NDA in common technical document (CTD) format with the archival copy submitted in electronic format in accordance with the January 1999 *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – NDAs*.

Case report forms and case report tabulations will be provided in electronic format only.
Does FDA require a paper copy of any of the technical sections (Modules 3, 4 and 5)?

FDA Response:

While you are not required to provide paper copies, desk copies would be appreciated as a review aid.

Additional Comment:

You should start considering a name for your dosage form that conforms to recognized standard dosage form names. (Please refer to the USP chapter "Pharmaceutical Dosage Forms" <1151>.)

b(4)

Discussion Point:

Action item: Sponsor will send the Agency clarification of the proposal in a few days.

Appears This Way
On Original

OLD Format

Division of Gastrointestinal & Coagulation Drug Products

ADMINISTRATIVE REVIEW OF NEW DRUG APPLICATION

Application Number: 22-020

Name of Drug: Protonix (pantoprazole sodium) Delayed Release 20 mg 40 mg

Sponsor: Wyeth Pharmaceuticals

Material Reviewed

Type of Submission: Electronic

Submission Date: May 12, 2006

Receipt Date: May 15, 2006

Filing Date: July 14, 2006

User-fee Goal Date(s): March 15, 2007

Proposed Indication: Short-term treatment of patients with gastroesophageal reflux disease (GERD) and a history of erosive esophagitis (EE). Maintenance of healing of EE, and long-term treatment of pathological hypersecretory conditions.

Other Background Information: This application is organized using the electronic Common Technical Document (eCTD) format and was submitted as a 505(b)(1) application with half fee payment based on bioavailability/bioequivalence data only. Wyeth Pharmaceuticals is the sponsor for NDA 20-987 Protonix (pantoprazole sodium) Delayed-Release Tablets, 20 mg and 40 mg tablets, approved on February 2, 2000. NDA 20-987 is approved for: short-term treatment of Erosive Esophagitis associated with Gastroesophageal Reflux Disease (GERD); maintenance of healing of erosive esophagitis; and pathological hypersecretory conditions including Zollinger-Ellison Syndrome. Wyeth Pharmaceuticals is also the sponsor of NDA 20-988 for Protonix I.V. (pantoprazole sodium) for injection, 40 mg, approved on March 22, 2001. NDA 20-988 is approved for: gastroesophageal reflux disease associated with a history of erosive esophagitis; and pathological hypersecretion associated with Zollinger-Ellison Syndrome.

Review

PART I: OVERALL FORMATTING^{a,d,e}

[Note: Items 1,2,3,4, & 5 must be submitted in paper.]	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
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1. Cover Letter	X	Electronic: Regional Information; Cover Letters
2. Form FDA 356h (original signature)	X	Regional Information: Forms
a. Establishment information	X	356h.pdf.page 3
b. Reference to DMF(s) & Other Applications	X	356h, page 1
3. User Fee FDA Form 3397	X	Electronic: Regional Information; Forms.
4. Patent information & certification	X	Electronic: Regional Information; Administrative Information; Patent Exclusivity
5. Debarment certification (Note: Must have a definitive statement)	X	Electronic: Regional Information; Administrative Information; Debarment Certification.
6. Field Copy Certification	X	X Electronic. TM 8/28/06
7. Financial Disclosure	X	Electronic: Regional Info: Administrative Info; Financial Disclosure.
8. Comprehensive Index	X	
9. Pagination	X	
10. Summary Volume	X	Common Technical Document Summaries 2.2 Introduction to Summaries, p. 1-17
11. Review Volumes	X	All electronic
12. Labeling (PI, container, & carton labels)	X	Electronic: Regional Info; Labeling
a. unannotated PI	X	Electronic: Labeling; Draft Labeling Text; PDF OK; WORD Repaired 7/31/06..
b. annotated PI	X	Electronic: Labeling; Annotated Draft Labeling Text; PDF OK; WORD Repaired 7/31/2006
c. immediate container	X	Electronic: Regional Info.; Labeling.
d. carton	X	Electronic, Regional Info.; Labeling.

e. patient package insert (PPI)		X	N/A
f. foreign labeling (English translation)		X	
13. Case Report Tabulations (CRT) (paper or electronic) (by individual patient data listing or demographic)	X		Electronic: Regional Info.; Clinical Study Reports; Reports of Biopharmaceutic Studies; Comparative BA and BE Study Reports; Data Tabulation
14. Case Report Forms (paper or electronic) (for death & dropouts due to adverse events)	X		Electronic: Regional Info.; Clinical Study Reports; Reports of Biopharmaceutic Studies; Case Report Forms

Y=Yes (Present), N=No (Absent)

Appears This Way
On Original

PART II: SUMMARY^{b,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. Pharmacologic Class, Scientific Rationale, Intended Use, & Potential Clinical Benefits	X		Electronic: Regional Information; CTD Summaries; Clinical Overview
2. Foreign Marketing History	X		Electronic: Regional Info.; Annual Report; Foreign Marketing History p.1-15.
3. Summary of Each Technical Section			
a. Chemistry, Manufacturing, & Controls (CMC)	X		Electronic: Common Technical Document Summaries; Quality Overall Summary
b. Nonclinical Pharmacology/Toxicology	X		Electronic: Common Technical Document Summaries; Bibckubucak Ivervew
c. Human Pharmacokinetic & Bioavailability	X		Electronic: CTD Summaries; Clinical Summary; Summary of Biopharmaceutics Studies
d. Microbiology			N/A
e. Clinical Data & Results of Statistical Analysis	X		CTD Summaries; Clinical Summary; Summary of Clinical Efficacy
4. Discussion of Benefit/Risk Relationship & Proposed Postmarketing Studies	X		Electronic: CTD Summaries; Introduction
5. Summary of Safety	X		Electronic: CTD Summaries; Clinical Summary; Summary of Clinical Safety
6. Summary of Efficacy	X		Electronic: CTD Summaries; Clinical Summary; Summary of Clinical Efficacy

Y=Yes (Present), N=No (Absent)

PART III: CLINICAL/STATISTICAL SECTIONS^{c,d,e}

	Y	N	COMMENTS (If paper: list volume & page numbers) (If electronic: list folder & page numbers)
1. List of Investigators		X	Not found.
2. Controlled Clinical Studies	X		Electronic: CTD Under Common Technical Document Summaries is a section: "Clinical Summary"; 5 Clinical Study Reports
a. Table of all studies	X		Electronic: CTD Summaries; Clinical Study Reports; Tabular Listing of All Clinical Studies
b. Synopsis, protocol, related publications, list of investigators, & integrated clinical & statistical report for each study (including completed, ongoing, & incomplete studies)	X		Regional Info; Clinical Study Reports; Reports of Biopharmaceutic Studies (see individual study reports)
c. Optional overall summary & evaluation of data from controlled clinical studies		X	N/A
3. Integrated Summary of Efficacy (ISE)	X		Electronic: CTD Summaries; Clinical Summary; Summary of Clinical Efficacy
4. Integrated Summary of Safety (ISS)	X		Electronic: CTD summaries; Clinical Summary; Summary of Clinical Safety
5. Drug Abuse & Overdosage Information		X	N/A
6. Integrated Summary of Benefits & Risks of the Drug	X		Electronic: CTD Summaries; Introduction
7. Gender/Race/Age Safety & Efficacy Analysis of Studies		X	N/A

Y=Yes (Present), N=No (Absent)

PART IV: MISCELLANEOUS^{d,e}

	Y	N	COMMENTS (list volume & page numbers) (If electronic: list folder & page numbers)
1. Written Documentation Regarding Drug Use in the Pediatric Population		X	Requesting Deferral of Pediatric Studies
2. Review Aids (Note: In electronic submission, can only request aids if increase functionality. In paper submission, verify that aids contain the exact information duplicated on paper. Otherwise, the aids are considered electronic submissions.)			
a. Proposed unannotated labeling in MS WORD	X		Unable to open WORD file without the assistance of FDA OIT repair to WORD Copy.
b. Stability data in SAS data set format (only if paper submission)		X	N/A
c. Efficacy data in SAS data set format (only if paper submission)		X	N/A
d. Biopharmacological information & study summaries in MS WORD (only if paper submission)		X	N/A
e. Animal tumorigenicity study data in SAS data set format (only if paper submission)		X	N/A
3. Exclusivity Statement (optional)	X		Electronic: Regional Information; Patent Exclusivity; Exclusivity Request

Y=Yes (Present), N=No (Absent)

^a [GUIDELINE ON FORMATTING, ASSEMBLING, AND SUBMITTING NEW DRUG AND ANTIBIOTIC APPLICATIONS] (FEBRUARY 1987).

^b“GUIDELINE FOR THE FORMAT AND CONTENT OF THE SUMMARY FOR NEW DRUG AND ANTIBIOTIC APPLICATIONS” (FEBRUARY 1987).

^c“GUIDELINE FOR THE FORMAT AND CONTENT OF THE CLINICAL AND STATISTICAL SECTIONS OF NEW DRUG APPLICATIONS” (JULY 1988).

^d“GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-GENERAL CONSIDERATIONS” (JANUARY 1999).

^e“GUIDANCE FOR INDUSTRY: PROVIDING REGULATORY SUBMISSIONS IN ELECTRONIC FORMAT-NDAS” (JANUARY 1999).

Additional Comments: N/A

Conclusions

Mary M. Lewis, RN
Regulatory Project Manager
8/28/06

cc:

Original NDA
HFD-180/Div. Files
HFD-180/RPM/
HFD-180/Talarico
HFD-180/Reviewers
draft:
r/d Initials:
final:
ADMINISTRATIVE REVIEW

Revised 9/29/00

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Lewis
8/28/2006 01:20:11 PM
CSO

Mary Lewis
8/28/2006 01:24:16 PM
CSO