CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-987/S-007

CORRESPONDENCE

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

June 8, 2001

NDA No. 20-987 Efficacy Supplement
PROTONIX® (pantoprazole sodium)
Delayed-Release Tablets

User Fee Payment
User Fee ID No. 4155

Food and Drug Administration (360909)
Mellon Client Service Center rm. 670
Pittsburgh, PA 15262-0001

Dear Sir or Madam:

Reference is made to the efficacy supplement to PROTONIX® (pantoprazole sodium) Delayed-Release Tablets NDA No. 20-987 for the indication of treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome, which is planned for submission in June 2001. This submission is a supplement that requires clinical data.

Enclosed is full payment of the required application fee ($154,823) for the above-referenced application. In addition, a copy of the User Fee cover sheet for this NDA supplement is also enclosed.

Please provide a receipt for the enclosed payment; a pre-addressed envelope is included for your convenience. If you have any questions regarding this payment, please contact me at (610) 902-3729.

Sincerely,

WYETH-AYERST LABORATORIES

Caroline M. Henesey

Caroline M. Henesey, Ph.D.
Manager, Worldwide Regulatory Affairs

Jab/173
Attachments

cc: Dr. L. Talarico, Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Ms. C. Perry, Project Manager, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

LTH-1019

WYETH-AYERST RESEARCH

P.O. BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

June 21, 2001

NDA No. 20-987 **Efficacy Supplement**
PROTONIX® (pantoprazole sodium)
Delayed-Release Tablets

Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Center for Drug Evaluation and Research
Attn: Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. Talarico:

Reference is made to Wyeth-Ayerst's (W-A's) New Drug Application No. 20-987 for PROTONIX® (pantoprazole sodium) Delayed-Release Tablets approved by the Division of Gastrointestinal and Coagulation Drug Products (DGCDP) on February 2, 2000. The purpose of this submission is to supplement NDA No. 20-987 to support PROTONIX Delayed-Release Tablets for the indication of treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome (ZES).

Submission Information

The archival copy of this submission, which includes Items 1-4, 6, 8/10 and 11-20, is provided in electronic format consistent with the "Guidance to Industry: Providing Regulatory Submissions in Electronic Format-NDAs" issued January 1999. An electronic regulatory review aid containing a Word 97 version of the proposed labeling is provided in Item 2. Case report tabulations for Protocol No. 3001A1-307-US, which provides the primary evidence of safety and efficacy in this supplement, are provided in Item 11 in SAS transport format. Case report tabulations for two Byk Gulden supportive studies in the ZES population, Study Nos. ——— and FK3038, are not available in SAS transport format. Therefore, the data from these studies are provided in PDF format in Item 11. A bibliography on literature citations of pantoprazole conducted by W-A is provided in Item 20.

This electronic archive copy of the submission is provided on 1 CD containing approximately 569 Megabytes. Please note that all files were scanned for viruses using McAfee VirusScan (version 4.0.3a) software and no viruses were detected. Paper copies of the sections requiring signatures (Items 13, 14, and 16-19) accompany the archive copy. One archival copy was submitted to the FDA/CDER Central Electronic File Room for uploading onto the FDA network. One review copy (in paper format) of Item 2 (Labeling), Item 3 (Application Summary) and each

of the applicable technical sections (Items 4, 6, and 8/10) is also being submitted to the DGCDP's Document Control Room (6B-24). A total of 18 volumes is provided.

In compliance with 21 CFR 314.50(k)(3), a duplicate copy of the Chemistry, Manufacturing, and Controls technical section, plus the application form and summary section of this supplement to NDA No. 20-987 were submitted to the Philadelphia District Office of the FDA. The requisite certification concerning this field copy is contained in Item 17. The debarment certification required under the Generic Drug Enforcement Act of 1992 is contained is Item 16. Financial disclosure information from the investigators conducting Protocol No. 3001A1-307-US, that provides the primary efficacy and safety data in this supplement, is provided in Item 19.

User Fee ID No. 4155 has been pre-assigned to this application. A check for the full application user fee (amount of $154,823.00) for this efficacy supplement was transmitted to Mellon Client Service Center Rm. 670, Pittsburgh, PA 15262-0001 on June 8, 2001.

Regulatory History

Wyeth-Ayerst submitted Protocol No. 3001A1-307-US to ~~IND No. 35,441 on~~ December 12, 1997 (Serial No. 083). The objective of this open-label pivotal study was to evaluate the safety and efficacy of long-term (up to 3 years) administration of pantoprazole tablets in patients with ZES or other hypersecretory conditions. On November 25, 1998, W-A submitted a justification to provide the results of this single oral pantoprazole study as primary evidence of safety and efficacy in order to obtain an additional indication for pantoprazole tablets in the treatment of ZES patients. This rationale referenced the April 29, 1997 meeting between the Agency and W-A, during which it was agreed that a single study using *intravenous* pantoprazole to treat 12 ZES patients (Protocol No. 3001K1-304-US) could be adequate to support a NDA provided there were highly compelling results with regard to efficacy. Since Protocol No. 3001A1-307-US had twice the number of patients as the intravenous study, W-A believed that pursuing an indication for oral pantoprazole based up on the results of this single study was justified. The Agency responded in a February 4, 1999 letter that it had reviewed the submission and concurred with W-A's proposal for a single study in ZES patients provided that:

- The study is conducted in 25 patients with a confirmed diagnosis of ZES,
- Patient evaluations, including endoscopy, are conducted at baseline and at least 6 months after initiation of therapy,
- Pharmacodynamic responses are titrated up and down so as to consider both higher effective doses and maintenance doses, and
- The study is conducted by investigators who are experts in the treatment of ZES.

Ø IES
Ø ISS
Full safety summary in Safety Summary

These issues were addressed with the conduct of Protocol No. 3001A1-307-US.

Primary Clinical Study Supporting Safety and Efficacy

One clinical study, Wyeth-Ayerst Protocol No. 3001A1-307-US, carried out in patients with ZES with or without multiple endocrine neoplasia type I (MEN-I), provides primary evidence of

efficacy and safety of pantoprazole tablets for long-term treatment of pathological hypersecretory conditions, including ZES. This was an open-label, multicenter study in which dosage regimens of oral pantoprazole were individually titrated based on the results of acid output measurements during the study. Oral pantoprazole at dosages ranging from 40 mg BID to 120 mg BID was effective at suppressing acid output for up to six months in patients with pathological hypersecretory conditions including ZES. Pantoprazole was safe and well tolerated in the long-term treatment of patients with pathological hypersecretory conditions, including ZES.

Since there is only one study providing the primary evidence of safety and efficacy for this supplement, integration of clinical data is not applicable. Therefore, an Integrated Summary of Efficacy and an Integrated Summary of Safety have not been provided. The safety and efficacy data from Protocol No. 3001A1-307-US are presented in this supplement in the final study report (CSR-37322) located in Item 8 and are summarized in Item 3 (Application Summary), Section 8 (Clinical Data Summary and Results of Statistical Analysis). Supportive efficacy and safety data from two Byk Gulden studies in the ZES population, [redacted] and FK3038, are summarized in Item 3 (Application Summary), Section 8.2.2.3 (Summary of Byk Gulden Efficacy Data) and Section 8.3 (Summary of Clinical Safety), respectively. In addition, this supplement contains supportive safety information derived from a total of 2661 patients in the gastroesophageal reflux disease (GERD) [acute treatment and maintenance of healing], *Helicobacter pylori*, and duodenal ulcer populations who participated in five W-A and 13 Byk Gulden studies. These data are presented in Item 3, Section 8.3 (Summary of Clinical Safety).

Pediatric Information

On February 13, 2001 W-A requested a waiver for the conduct of clinical trials of hypersecretory conditions, including ZES, in the pediatric population. Since the incidence of this condition in pediatric patients is below the substantial number of patients needed, there is reasonable basis to conclude that the necessary pediatric studies are impossible or highly impractical to conduct. The DGCDP issued the requested waiver on April 2, 2001. A copy of the DGCDP's letter is provided in Item 20 Other.

If there are any questions regarding this submission, please contact me at (484) 865-3729.

Sincerely,

WYETH-AYERST LABORATORIES

Caroline M. Henesey

Caroline M. Henesey, Ph.D.
Manager, Worldwide Regulatory Affairs

Enclosure
Jab/177

cc: Ms. Cheryl Perry, Project Manager, DGCDP, HFD-180

WYETH-AYERST RESEARCH

PO BOX 8299 • PHILADELPHIA, PA 19101-8299

Division of American Home Products Corporation

WORLDWIDE REGULATORY AFFAIRS

March 1, 2002

NDA No. 20-987/S-007
PROTONIX® (pantoprazole sodium)
Delayed-Release Tablets

Amendment to Pending
New Drug Application Supplement
Updated Proposed Package Insert Labeling

Victor Raczkowski, M.D., Acting Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Center for Drug Evaluation and Research
Attn: Document Control Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

NDA SUPPLEMENT

SE1-007-BL

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 04 2002
HFD-180

Dear Dr. Raczkowski:

Reference is made to our June 21, 2001 supplement to New Drug Application No. 20-987 (S-007) for PROTONIX® (pantoprazole sodium) Delayed-Release Tablets for the indication of ~~long-term~~ treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome. The purpose of this submission is to provide an updated version of the proposed package insert labeling which (1) reflects changes that were approved by the Division of Gastrointestinal and Coagulation Drug Products since submission of this supplement, and (2) proposes changes to harmonize the PROTONIX Tablets labeling with the currently approved labeling for PROTONIX® I.V. (pantoprazole sodium) for Injection (approved on October 19, 2001).

Accordingly, please find the updated version of proposed labeling for PROTONIX Tablets as Attachment A. This labeling reflects the following:

- June 12, 2001 approval of the maintenance of healing indication (NDA No. 20-987/S-001) and 20 mg tablet strength for PROTONIX Tablets,
- July 20, 2001 approval of the April 25, 2001 supplement to NDA No. 20-987 (S-004) revising the OVERDOSAGE section of the labeling for PROTONIX Tablets.
- Proposed text to harmonize the PROTONIX Tablets labeling with labeling approved on October 19, 2001 (NDA No. 20-988/S-003) for PROTONIX I.V. with regards to the indication of treatment of pathological hypersecretory conditions associated with Zollinger-Ellison Syndrome or other neoplastic conditions. Proposed additions are double-underlined and deletions are in strikethrough.
- This version also reflects Wyeth's proposals for incorporating the indication of treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome, which are

unchanged from the April 19, 2001 submission. Proposed additions are double-underlined and deletions are in strikethrough.

A Word 97 file and PDF version of this proposed labeling will be provided today to Ms. Cheryl Perry, Project Manager of the DGCDP, via confidential email. If you have any questions regarding this submission, please contact Mr. James Ciciriello at (484) 865-3757 or Dr. John J. Savarese at (484) 865-7013.

Sincerely,

WYETH-AYERST LABORATORIES

Caroline M. Henesey

Caroline M. Henesey, Ph.D.
Sr. Manager, Worldwide Regulatory Affairs

Attachment
CMH/317

16 pages redacted from this section of the approval package consisted of draft labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-987/S-007

PRIOR APPROVAL SUPPLEMENT

Wyeth-Ayerst Laboratories
Attention: Caroline M. Henesey, Ph.D.
Manager, Worldwide Regulatory Affairs
P.O. Box 8299
Philadelphia, PA 19101-8299

JUL - 2 2001

Dear Dr. Henesey:

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

Name of Drug Product: PROTONIX® (pantoprazole sodium) Delayed-Release Tablets, 20 mg and 40 mg

NDA Number: 20-987

Supplement Number: 007

Review Priority Classification: Standard (S)

Date of Supplement: June 21, 2001

Date of Receipt: June 22, 2001

This supplement proposes the following new indication for Protonix® tablets: "treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome (ZES)."

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 21, 2001 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 22, 2002 and the secondary user fee goal date will be June 22, 2002.

Be advised that, as of April 1, 1999, 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 (63 *FR* 66632). We acknowledge your February 13, 2001 correspondences to [redacted] requesting a waiver of the pediatric study requirement for this proposed indication. In an April 2, 2001 Agency letter, a waiver for pediatric studies for Protonix® (pantoprazole sodium) Delayed-Release Tablets was granted for the following indication: hypersecretory conditions, including Zollinger-Ellison syndrome.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. We acknowledge your January 19, 2001 "Proposed Pediatric Study Request" (PPSR). We are reviewing your submission and will respond to your proposal in a separate letter. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to a NDA. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room, 6B-24
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, please call me at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

Cheryl Perry
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Cheryl Perry
7/2/01 03:33:52 PM