

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-987/S-007

ADMINISTRATIVE DOCUMENTS

**TIME SENSITIVE PATENT INFORMATION PURSUANT TO 21 C.F.R. 314.53
for NDA 20-987**

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name: PROTONIX®
Active ingredient(s): pantoprazole sodium
Strength(s): 20 mg and 40 mg
Dosage Form: Tablet, Delayed Release, Oral
Approval Date: February 2, 2000

A. Information for each individual patent:

US Patent Number: 4,758,579
Expiration Date: July 19, 2005 (Patent Term Extension under 35 U.S.C. §156 has been requested)
Type of Patent: Drug Substance (Ingredient) – PROTONIX® oral tablet formulation
Patent Owner: Byk Gulden Lomborg Chemische Fabrik GmbH
US Agent: American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

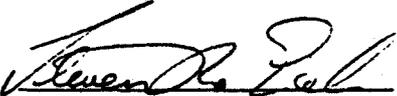
US Patent Number: 5,997,903
Expiration Date: December 7, 2116
Type of Patent: Drug Product (Composition/Formulation) – PROTONIX® oral tablet formulation
Patent Owner: American Home Products Corp., parent company of the Applicant, is the exclusive licensee under the patent.

B. Declaration statement for listed patents which have Composition/Formulation or Method of Use claims:

The undersigned declares that the above stated US Patent No. 4,758,579 covers the drug substance (ingredient) of PROTONIX®. This product is the subject of this application for which approval is being sought.

The undersigned declares that the above stated US Patent No. 5,997,903 covers the oral formulation of PROTONIX®. This product is the subject of this application for which approval is being sought.

WYETH-AYERST LABORATORIES

By: 
Steven R. Eck
Patent Counsel
Date: May 31, 2001

CONFIDENTIAL

Patent / Exclusivity Information

- | | |
|---|--|
| 1) Active ingredient(s) | Pantoprazole Sodium |
| 2) Strength(s) | 20 mg and 40 mg |
| 3) Trade Name | PROTONIX® |
| 4) Dosage Form
(Route of Administration) | Tablet, 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 approved
with an effective date which is prior to 3 years
after the date of approval of this NDA supplement. |
| 9) Applicable patent numbers
and expiration date of each | U.S. Patent 4,758,579,
Normal Expiration Date: July 19, 2005
U.S. Patent 5,997,903,
Normal Expiration Date: December 7, 2116 |

CONFIDENTIAL

FDA Links Searches Check Lists Tracking Links Calendars Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

NDA Number: 020987 **Trade Name:** PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
Supplement Number: 007 **Generic Name:** PANTOPRAZOLE SODIUM
Supplement Type: SE1 **Dosage Form:**
Regulatory Action: AP **COMIS Indication:** SHORT TERM TREATMENT OF EROSIVE ESOPHAGITIS ASSOCIATED WITH GASTROESOPHAGEAL REFLUX DISEASE
Original NDA Action Date: 4/19/02

Indication # 1 Pathological hypersecretory conditions including Zollinger-Ellison Syndrome.

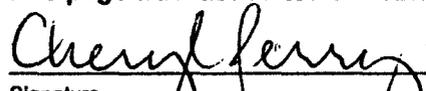
Comments (if any):

Ranges for This Indication

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
0 years	17 years	Waived	4/2/01

Comments: Too few affected children to study with these conditions.

This page was last edited on 4/22/02



 Signature
 Reg. Project Manager, HFD180

 Date
 22 April 2002

PROTONIX[®] (pantoprazole sodium) Delayed-Release Tablets

Supplement to 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 use in any capacity the services of any person debarred under subsection (a) or (b) [section 206 (a) or (b)] of the Generic Drug Enforcement Act of 1992 in connection with this supplement to NDA No. 20-987 for PROTONIX[®] (pantoprazole sodium) Delayed-Release Tablets for the indication of treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

Signed: Maureen D. Skowronek

**Maureen D. Skowronek
Assistant Vice President,
Global Product Development,
Worldwide Regulatory Affairs**

PROTONIX[®] (pantoprazole sodium) Delayed-Release Tablets

NDA No. 20-987 Supplement

**Item 17. Certification Required by New Drug and Abbreviated New Drug Applications
Preapproval Inspection Requirements**

The undersigned certifies that Wyeth-Ayerst has provided a field copy of the Chemistry, Manufacturing, and Controls section, application form, and application summary of this NDA No. 20-987 supplement for PROTONIX[®] (pantoprazole sodium) Delayed-Release Tablets for the indication of treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome to the Philadelphia District Office, the FDA home district office for Wyeth-Ayerst Laboratories, as required under 21 CFR 314.50 (d)(1)(v).

Signed: Maureen D. Skowronek
Maureen D. Skowronek
Assistant Vice President,
Global Product Development,
Worldwide Regulatory Affairs

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 checkboxes.

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 has 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 Oral Maintenance – ZES	Study 307 – US
(see attached lists)	

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)).

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 Joseph S. Camardo, MD Mr. Robert Haller		Title Senior Vice President – Clinical R & D Vice President – R & D Finance
Firm/Organization Wyeth – Ayerst Research		
Signature	Date	

Paperwork Reduction Act Statement

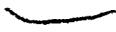
An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions,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

Please DO NOT RETURN this form to this address.

**Pantoprazole Oral Maintenance - ZES
Study 307-US**

The Clinical Investigators listed below include only those whose site enrolled patients in the above referenced study.

<i>Last Name</i>	<i>First</i>	<i>MI</i>
		
		
		

**Pantoprazole Oral Maintenance - ZES
Study 307-US**

Letters requesting financial Disclosure were sent to the Clinical Investigators listed below as their site enrolled patients in the above referenced study. If no response was received from the initial request, additional attempts were performed (such as mail, phone, fax, e-mail) in order to meet the Financial Disclosure requirement. See comments below for explanation as to why Financial Disclosure forms could not be obtained.

<i>Last Name</i>	<i>First</i>	<i>MI</i>	<i>Comments</i>
			No longer at site. Forwarding address not provided.
			No longer at site. Forwarding address not provided.
			No longer at site. Forwarding address not provided.
			No longer at site. Forwarding address provided.

**Pantoprazole Oral Maintenance-ZES
Study 307-US**

The following individuals were listed on Form 1572s; however, Financial Disclosure Forms were not received because they either did not participate in the study or the level of their involvement does not require the submission of Financial Disclosure Forms.

Last Name	First	MI
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_____	_____	_____
_____	_____	_____

Attachment I (Form FDA 356h) – Establishment Information

Pantoprazole sodium sesquihydrate drug substance for commercial use will be synthesized, tested and released by:

Byk Gulden Lomberg
Lomberg Chemische Fabrik GmbH
Robert-Bosch-Strasse #8
D-78224 Singen
Germany

DMF No.:
Registration No. of the German
Court of Trade: ~~HRB-12~~ Court of
Register Konstanz

Contact: Erich Rapp, Ph.D.
Phone: 49 (7531) 84-1369

The drug product will be manufactured by:

Byk Gulden, Oranienburg *
Lehnitzstrasse 70-98
D-16515 Oranienburg
Germany

Registration No. of the German
Court of Trade: HRB 45 Court of
Register Neurupin

Contact: Ms. Christine Melms, Pharmacist
Phone: 49 (3301) 818-443

* Also denoted as Oranienburger Pharmawerk GmbH (OPW). The facilities are one and the same.

PROTONIX Tablets will be tested, packaged and released by:

Wyeth Pharmaceuticals Co. (WPC)**
Highway No. 3, Km 142.1
Barrios Pozo Hondos and Jobos
Guayama, Puerto Rico 00785

Registration No.: 2650135
DMF No.:

Contact: Mr. Mariano Martinez-Mora
Phone: 787-866-7250

** Formerly known as Ayerst-Wyeth Pharmaceuticals Inc. (AWPI)

The preapproval inspection for NDA No. 20-987 for PROTONIX (pantoprazole sodium) Delayed-Release Tablets was performed in September 1998. Since this is an efficacy supplement to NDA No. 20-987, an additional inspection is not required/anticipated.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS Wyeth-Ayerst Laboratories P.O. Box 8299 Philadelphia, PA 19101-8299		3. PRODUCT NAME PROTONIX® (pantoprazole sodium) Delayed-Release Tablets for treatment of pathological hypersecretory conditions
2. TELEPHONE NUMBER (Include Area Code) (610) 902-3729		4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION. <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO (APPLICATION NO. CONTAINING THE DATA).
5. USER FEE I.D. NUMBER 4155	6. LICENSE NUMBER / NDA NUMBER NO20-987	

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

<input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory)	<input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (See Item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetics Act (See Item 7, reverse side before checking box.)	<input type="checkbox"/> THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (See Item 7, reverse side before checking box.)
<input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY (Self Explanatory)	

FOR BIOLOGICAL PRODUCTS ONLY

<input type="checkbox"/> WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION	<input type="checkbox"/> A CRUDE ALLERGENIC EXTRACT PRODUCT
<input type="checkbox"/> AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY	<input type="checkbox"/> AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT
<input type="checkbox"/> BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92	

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? YES NO
(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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.

Please **DO NOT RETURN** this form to this address.

NATURE OF AUTHORIZED COMPANY REPRESENTATIVE C. Coline M. Henesey, Ph.D.	TITLE Manager, Worldwide Regulatory Affairs	DATE 6/7/01
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K3.1A

Document Assignment Report

N20987

REC: 4/24/ 1 218 001



K3.1A

tatus/Dt: AP APPROVED

02-F



N20987

001

ABS

Let/Phone Dt: 30-JUN-1998

Primary Goal Dt: 03-FEB-2000

Name: PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE

Div: 180

Secondary Goal Dt: 03-FEB-2000

Doc Type: SE1 Doc Seq#: 007 Doc Mod Type: Letter Dt: 21-JUN-2001 Stamp Dt: 22-JUN-2001

Dec Code: OP OPEN

Dec Dt: 22-JUN-2001

Due Dt: 19-DEC-2001

DDR Dt: 25-JUN-2001

Safety/Filing Dt: 21-AUG-2001

Primary Goal Dt: 22-APR-2002

Div Goal Dt:

Action Pref Goal Dt:

Secondary Goal Dt: 22-JUN-2002

Subpart H: N Priority: X LVP: X Small Business: X Billable: Y Feemod: 0 Prior Approv:

Clinical: X Waiver: X Type 6:

UFID Type:

Fee 505B2: X User Fee ID:

Reviewer Code/Name	Con	Disc	Assign Date	Rev-Start	Rev-Final	Sup-Concur	St	Ext
89Q JOSEPH, RAYMOND	N	MDO	25-JUN-2001				OP	0
88E KOWBLANSKY, MARI	N	CHM	25-JUN-2001				OP	0
89P PERRY, CHERYL	N	CSO	25-JUN-2001				OP	0
99F PERMUTT, THOMAS	N	STT	25-JUN-2001				OP	0

Doc Type: SE1

Seq No: 007

Doc Mod Type:

From Stamp Date:

To Stamp Date:

Typ	Seq#	Mod Type	Letter Date	Stamp Date	Decision	Dec Date	Status	Status Date
SE1	007		21-JUN-2001	22-JUN-2001	OP	22-JUN-2001	PN	22-JUN-2001
SE1	007	SU	22-OCT-2001	23-OCT-2001	OP	23-OCT-2001		
SE1	007	BL	01-MAR-2002	04-MAR-2002	OP	04-MAR-2002		
SE1	007	BM	18-MAR-2002	19-MAR-2002	OP	19-MAR-2002		

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-987	Efficacy Supplement Type SE-1	Supplement Number 007
Drug: PROTONIX® (pantoprazole sodium) Delayed-Release Tablets		Applicant: Wyeth-Ayerst Laboratories
RPM: Cheryl Perry	HFD-180	Phone # 301-827-7475
Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)		Reference Listed Drug (NDA #, Name): Not applicable
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		Proton pump inhibitor
❖ User Fee Goal Date		April 22, 2002
❖ Special programs (indicate all that apply)		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid \$154,823 June 8, 2001
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) <input type="checkbox"/> Other
❖ Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• This application is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
• Exception for review (Center Director's memo)		Not applicable
• OC clearance for approval		Not applicable
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.		<input checked="" type="checkbox"/> Verified
❖ Patent		
• Information: Verify that patent information was submitted		<input checked="" type="checkbox"/> Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted		21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> III <input type="checkbox"/> IV 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		<input type="checkbox"/> Verified

❖ Exclusivity (approvals only)	
• Exclusivity summary	<input checked="" type="checkbox"/> Yes
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!	() Yes, Application # _____ <input checked="" type="checkbox"/> No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	Project Manager: July 10, 2001
General Information	
❖ Actions	
• Proposed action	<input checked="" type="checkbox"/> AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	None
• Status of advertising (approvals only)	<input checked="" type="checkbox"/> Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes <input checked="" type="checkbox"/> Not applicable
• Indicate what types (if any) of information dissemination are anticipated	<input checked="" type="checkbox"/> None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Not applicable
• Most recent applicant-proposed labeling	March 1, 2002
• Original applicant-proposed labeling	June 21, 2001
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings (indicate dates of reviews and meetings)	RPM Labeling Review: April 19, 2002
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	None
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Not applicable
• Applicant proposed	Not applicable
• Reviews	Not applicable
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	None
• Documentation of discussions and/or agreements relating to post-marketing commitments	None
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	July 2, 2001: acknowledgement letter
❖ Memoranda and Telecons	None
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	Not applicable
• Pre-NDA meeting (indicate date)	Not applicable
• Pre-Approval Safety Conference (indicate date; approvals only)	Not applicable
• Other	Not applicable

❖ Advisory Committee Meeting	
• Date of Meeting	Not applicable
• 48-hour alert	Not applicable
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	Not applicable
Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Medical Team Leader: April 2, 2002
Clinical Information	
❖ Clinical review (indicate date for each review)	April 2, 2002
❖ Microbiology (efficacy) review (indicate date for each review)	Not applicable
❖ Safety Update review (indicate date or location if incorporated in another review)	Located in Clinical review dated April 2, 2002
❖ Pediatric Page (separate page for each indication addressing status of all age groups)	<input checked="" type="checkbox"/> Yes
❖ Statistical review (indicate date for each review)	Not applicable
❖ Biopharmaceutical review (indicate date for each review)	Not applicable
❖ Controlled Substance Staff review and recommendation for scheduling (indicate date for each review)	Not applicable
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	Not applicable
• Bioequivalence studies	Not applicable
CMC Information	
❖ CMC review (indicate date for each review)	February 15, 2002
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	February 15, 2002
• Review & FONSI (indicate date of review)	Not applicable
• Review & Environmental Impact Statement (indicate date of each review)	Not applicable
❖ Micro (validation of sterilization & product sterility) review	Not applicable
❖ Facilities inspection (provide EER report)	Date completed: () Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested <input checked="" type="checkbox"/> Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review, including referenced IND reviews (indicate date for each review)	Not applicable
❖ Nonclinical inspection review summary	Not applicable
❖ Statistical review of carcinogenicity studies (indicate date for each review)	Not applicable
❖ CAC/ECAC report	Not applicable

**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

4/22/02 01:56:36 PM

Division of Gastrointestinal & Coagulation Drug Products
CONSUMER SAFETY OFFICER REVIEW

APR 19 2002

Application Number: **NDA 20-987/SE1-007**
Name of Drug: **PROTONIX® (pantoprazole sodium) Delayed-Release Tablets, 20 mg and 40 mg**
Sponsor: **Wyeth-Ayerst Research**

Material Reviewed

Submission Date: **March 1, 2002**
Receipt Date: **March 4, 2002**

Background and Summary Description:

June 12, 2001 – Approval of SE1-001 for the new indication for long-term maintenance of healing of Erosive Esophagitis, and a 20 mg tablet strength.

June 22, 2001 – SE1-007 submitted. Provided for a new indication for treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

July 20, 2001 – Approval of SLR-005 revising the OVERDOSAGE section of the package insert.

Review

PACKAGE INSERT TEXT

Package insert text currently approved on draft July 20, 2001 (S-005) was compared with proposed draft labeling submitted March 4, 2002.

The text is identical except for the following:

Revised Section	Exact Location	Revision	Recommendation
CLINICAL PHARMACOLOGY; Drug-Drug Interactions	7 th sentence added	To read: "Although no significant drug-drug interactions have been observed in clinical studies, the potential for significant drug-drug interactions with more than once daily dosing with high doses of pantoprazole has not been studied in poor metabolizers or individuals who are hepatically impaired."	This addition was reviewed by Suresh Doddapaneni, PhD, Biopharmaceutics Team Leader; Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE .

<p>CLINICAL PHARMACOLOGY; Pharmacodynamics; <i>Mechanism of Action</i></p>	<p>Stand-alone paragraph revised to read:</p>	<p>"Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalently bond-binding to two sites of the (H⁺,K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H⁺,K⁺)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours <u>for all doses tested.</u>"</p>	<p>This revision was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>
<p>Clinical Studies</p>	<p>New subsection added to read:</p>	<p>"Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome In a multicenter, open-label trial of 35 patients with pathological hypersecretory conditions, such as Zollinger-Ellison syndrome with or without multiple endocrine neoplasia-type I, PROTONIX successfully controlled gastric acid secretion. Doses ranging from 80 mg daily to 240 mg daily maintained gastric acid output below 10 mEq/h in patients without prior acid-reducing surgery and below 5 mEq/h in patients with prior acid-reducing surgery. Doses were initially titrated to the individual patient needs, and adjusted in some patients based on the clinical response with time. (See DOSAGE AND ADMINISTRATION.) PROTONIX was well tolerated at these dose levels for prolonged periods (greater than 2 years in some patients)."</p>	<p>This addition was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>
<p>INDICATIONS AND USAGE</p>	<p>New subsection added to read:</p>	<p>"Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome PROTONIX Delayed-Release Tablets are indicated for the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome."</p>	<p>This addition was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>
<p>PRECAUTIONS; Drug Interactions</p>	<p>2nd paragraph revised to read:</p>	<p>"Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts)."</p>	<p>This revision was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>

<p>ADVERSE REACTIONS</p>	<p>Added paragraph to end of section to read:</p>	<p>"In an open-label US clinical trial conducted in 35 patients with pathological hypersecretory conditions treated with PROTONIX for up to 27 months, the adverse events reported were consistent with the safety profile of the drug in other populations."</p>	<p>This addition was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>
<p>ADVERSE REACTIONS; Postmarketing Reports</p>	<p>Added one word to read:</p>	<p>"There have been spontaneous reports of adverse events with the post-marketing use of pantoprazole. These reports include anaphylaxis (including anaphylactic shock); angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatological reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); hepatocellular damage leading to jaundice and hepatic failure; pancreatitis; <u>pancytopenia</u>; and rhabdomyolysis."</p>	<p>This addition was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>
<p>ADVERSE REACTIONS; Laboratory Values</p>	<p>1st two sentences were revised to read:</p>	<p>"In two U.S. controlled, short-term trials <u>in patients with erosive esophagitis associated with GERD</u>, 0.4 % of the patients on PROTONIX 40 mg experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. In two U.S. controlled, long-term trials <u>in patients with erosive esophagitis associated with GERD</u>, none of 178 patients (0%) on PROTONIX 40 mg and two of 181 patients (1.1%) on PROTONIX 20 mg, experienced significant transaminase elevations at 12 months (or earlier if a patient discontinued prematurely)."</p>	<p>This revision was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>
<p>DOSAGE AND ADMINISTRATION</p>	<p>New subsection added to read:</p>	<p>"Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome The dosage of PROTONIX in patients with pathological hypersecretory conditions varies with the individual patient. The recommended adult starting dose is 40 mg twice daily. Dosage regimens should be adjusted to individual patient needs and should continue for as long as clinically indicated. Doses up to 240 mg daily have been administered. Some patients have been treated continuously with PROTONIX for more than 2 years."</p>	<p>This addition was reviewed by Robert Prizont, MD, Medical Reviewer; and Hugo Gallo-Torres, MD, PhD and it is ACCEPTABLE.</p>

Conclusion

The identified labeling changes are **ACCEPTABLE**. An approval letter can be issued.

{See appended electronic signature page}

Cheryl Perry
Regulatory Health Project Manager

Joyce Korvick, MD
Deputy Division Director

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R/d Initials: J. Korvick/April 18, 2002
Final: C.Perry/April 19, 2002
Filename: N20987.s007.LabelRev.doc

CSO REVIEW

Labeling Changes Proposed in This Submission

The labeling changes to the PROTONIX® (pantoprazole sodium) Delayed-Release Tablets package insert proposed in this submission provide for the incorporation of the indication for treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. These changes impact the **CLINICAL PHARMACOLOGY, INDICATIONS AND USAGE, ADVERSE REACTIONS AND DOSAGE AND ADMINISTRATION** sections. Changes in addition to those related to the proposed indication are discussed below (Section 1.4). Specific changes proposed to the labeling text are indicated by double underline (additions) and strikethrough (deletions). The carton and container labeling for PROTONIX® Delayed-Release Tablets are not impacted by this supplement.

Dates of Last Approved Labeling

The last approved labeling for PROTONIX® (pantoprazole sodium) Delayed-Release Tablets was approved on May 21, 2001 as part of the approval of NDA No. 20-987/S-004, providing for the deletion of text pertaining to dose adjustment for patients with renal or hepatic impairment, or elderly patients.

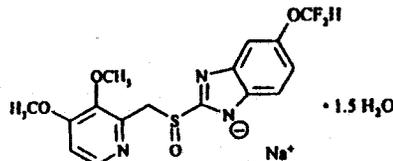
History of All Changes Since Last Approved Labeling

As of June 5, 2001, there have been no changes since the last approved PROTONIX® (pantoprazole sodium) Delayed-Release Tablets labeling on May 21, 2001.

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

W
PROTONIX®
(pantoprazole sodium)
Delayed-Release Tablets

DESCRIPTION
The active ingredient in PROTONIX® (pantoprazole sodium) Delayed-Release Tablets is a substituted benzimidazole, sodium 5-(difluoromethoxy)-2-[(3,4-dimethoxy-2-pyridinylmethyl) sulfinyl]-1H-benzimidazole sesquihydrate, a compound that inhibits gastric acid secretion. Its empirical formula is C₁₈H₁₄F₂N₂NaO₈S x 1.5 H₂O, with a molecular weight of 432.4. The structural formula is:



Pantoprazole sodium sesquihydrate is a white to off-white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in n-hexane.

The stability of the compound in aqueous solution is pH-dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8.

PROTONIX 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) with the following inactive ingredients: anhydrous sodium carbonate NF, mannitol USP, croscopolidone NF, povidone USP, calcium stearate NF, hydroxypropyl methylcellulose USP, titanium dioxide USP, yellow iron oxide NF, propylene glycol USP, methacrylic acid copolymer NF, polysorbate 80 NF, sodium lauryl sulfate NF, and triethyl citrate NF.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Protonix is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. Peak serum concentration (C_{max}) and area under the serum concentration time curve (AUC) 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. Following oral or intravenous administration, the serum concentration of pantoprazole declines biexponentially with a terminal elimination half-life of approximately one hour. In extensive metabolizers (see Metabolism section) with normal liver function receiving an oral dose of the enteric-coated 40 mg pantoprazole tablet, the peak concentration (C_{max}) is 2.4 µg/mL, the time to reach the peak concentration (t_{max}) is 2.4 h and the total area under the plasma concentration versus time curve (AUC) is 4.8 µg·h/mL. When pantoprazole is given with food, its t_{max} is highly variable and may increase significantly. Following intravenous administration of pantoprazole to extensive metabolizers, its total clearance is 7.6-14.0 L/h and its apparent volume of distribution is 11.0-23.6L.

Absorption

The absorption of pantoprazole is rapid, with a C_{max} of 2.5 µg/mL that occurs approximately 2.5 hours after single or multiple oral 40-mg doses. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. 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.

Distribution

The apparent volume of distribution of pantoprazole is approximately 11.0-23.6L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism

Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (e.g. 3% of Caucasians and African-Americans and 17-23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation (≤ 23%) with once daily dosing.

Elimination

After a single oral or intravenous dose of ¹⁴C-labeled pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion. There was no renal excretion of unchanged pantoprazole.

Special Populations

Geriatric

Only slight to moderate increases in pantoprazole AUC (43%) and C_{max} (26%) were found in elderly volunteers (64 to 76 years of age) after repeated oral administration, compared with younger subjects. No dosage adjustment is recommended based on age.

Pediatric

The pharmacokinetics of pantoprazole have not been investigated in patients <18 years of age.

Gender

There is a modest increase in pantoprazole AUC and C_{max} in women compared to men. However, weight-normalized clearance values are similar in women and men. No dosage adjustment is needed based on gender (Also see Use in Women).

Renal Impairment

In patients with severe renal impairment, pharmacokinetic parameters for pantoprazole were similar to those of healthy subjects. No dosage adjustment is necessary in patients with renal impairment or in patients undergoing hemodialysis.

Hepatic Impairment

In patients with mild to severe hepatic impairment, maximum pantoprazole concentrations increased only slightly (1.5-fold) relative to healthy subjects. Although serum half-life values increased to 7-9 hours and AUC values increased by 5- to 7-fold in hepatic-impaired patients, these increases were no greater than those observed in slow CYP2C19 metabolizers, where no dosage frequency adjustment is warranted. These pharmacokinetic changes in hepatic-impaired patients result in minimal drug accumulation following once daily multiple-dose administration. No dosage adjustment is needed in patients with mild to severe hepatic impairment.

Drug-Drug Interactions

Pantoprazole is metabolized mainly by CYP2C19 and to minor extents by CYPs 3A4, 2D6 and 2C9. In *in vivo* drug-drug interaction studies with CYP2C19 substrates (diazepam [also a CYP3A4 substrate] and phenytoin [also a CYP3A4 inducer], nifedipine [a CYP3A4 substrate], metoprolol [a CYP2D6 substrate], diclofenac [a CYP2C9 substrate] and theophylline [a CYP1A2 substrate]) in healthy subjects, the pharmacokinetics of pantoprazole were not significantly altered. It is, therefore, expected that other drugs metabolized by CYPs 2C19, 3A4, 2D6, 2C9 and 1A2 would not significantly affect the pharmacokinetics of pantoprazole. *In vivo* studies also suggest that pantoprazole does not significantly affect the kinetics of other drugs (cisapride, theophylline, diazepam [and its active metabolite, desmethyldiazepam], phenytoin, warfarin, metoprolol, nifedipine, carbamazepine and oral contraceptives) metabolized by CYPs 2C19, 3A4, 2C9, 2D6 and 1A2. Therefore, it is expected that pantoprazole would not significantly affect the pharmacokinetics of other drugs metabolized by these isozymes. Dosage adjustment of such drugs is not necessary when they are co-administered with pantoprazole. In other *in vivo* studies, digoxin, ethanol, glyburide, antipyrine, and caffeine had no clinically relevant interactions with pantoprazole.

Packaging Insert
Revised March 27, 2001
APD SLR-004
on May 21, 2001
C1 6004-3

Pharmacodynamics

Mechanism of Action

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by forming a covalent bond to two sites of the (H⁺, K⁺)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect is dose-related and leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H⁺, K⁺)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours.

Antisecretory Activity

Under maximal acid stimulatory conditions using pentagastrin, a dose-dependent decrease in gastric acid output occurs after a single dose of oral (20-80 mg) or a single dose of intravenous (20-120 mg) pantoprazole in healthy volunteers. Pantoprazole given once daily results in increasing inhibition of gastric acid secretion. Following the initial oral dose of 40 mg pantoprazole, a 51% mean inhibition was achieved by 2.5 hours. With once a day dosing for 7 days the mean inhibition was increased to 85%. Pantoprazole suppressed acid secretion in excess of 95% in half of the subjects. Acid secretion had returned to normal within a week after the last dose of pantoprazole; there was no evidence of rebound hypersecretion.

In a series of dose-response studies pantoprazole, at oral doses ranging from 20 to 120 mg, caused dose-related increases in median basal gastric pH and in the percent of time gastric pH was > 3 and > 4. Treatment with 40 mg of pantoprazole produced optimal increases in gastric pH which were significantly greater than the 20-mg dose. Doses higher than 40 mg (60, 80, 120 mg) did not result in further significant increases in median gastric pH. The effects of pantoprazole on median pH from one double-blind crossover study are shown below.

Effect of Single Daily Doses of Oral Pantoprazole on Intra-gastric pH

Time	Median pH on day 7			
	Placebo	20 mg	40 mg	80 mg
8 a.m. - 8 a.m. (24 hours)	1.3	2.9*	3.8*	3.9*
8 a.m. - 10 p.m. (Daytime)	1.8	3.2*	4.4**	4.6**
10 p.m. - 8 a.m. (Nighttime)	1.2	2.1*	3.0*	2.6*

* Significantly different from placebo
 ** Significantly different from 20 mg

Serum Gastrin Effects

Fasting serum gastrin levels were assessed in two double-blind studies of the acute healing of erosive esophagitis (EE) in which 682 patients with gastroesophageal reflux disease (GERD) received 10, 20, or 40 mg of pantoprazole for up to 8 weeks. At 4 weeks of treatment there was an increase in mean gastrin levels of 7%, 35%, and 72% over pretreatment values in the 10, 20 and 40 mg treatment groups, respectively. A similar increase in serum gastrin levels was noted at the 8 week visit with mean increases of 3%, 26%, and 84% for the three pantoprazole dose groups.

In long term studies involving over 800 patients, a 2- to 3-fold mean increase from the pretreatment fasting serum gastrin level was observed in the initial months of treatment with pantoprazole at doses of 40 mg per day during GERD maintenance studies and 40 mg or higher per day in patients with refractory GERD. Fasting serum gastrin levels generally remained at approximately 2 to 3 times baseline for up to 4 years of periodic follow-up in clinical trials.

Following healing of gastric or duodenal ulcers with pantoprazole treatment, elevated gastrin levels return to normal by at least 3 months.

Enterochromaffin-Like (ECL) Cell Effects

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

In a nonclinical study in Sprague-Dawley rats, lifetime exposure (24 months) to pantoprazole at doses of 0.5 to 200 mg/kg/day resulted in dose-related increases in gastric ECL-cell proliferation and gastric neuroendocrine (NE)-cell tumors. Gastric NE-cell tumors in rats may result from chronic elevation of serum gastrin levels. The high density of ECL cells in the rat stomach makes this species highly susceptible to the proliferative effects of elevated gastrin levels produced by proton pump inhibitors.

However, there were no observed elevations in serum gastrin following the administration of pantoprazole at a dose of 0.5 mg/kg/day. In a separate study, a gastric NE-cell tumor without concomitant ECL-cell proliferative changes was observed in 1 female rat following 12 months of dosing with pantoprazole at 5 mg/kg/day and a 9 month off-dose recovery. (See PRECAUTIONS, Carcinogenesis, Mutagenesis, Impairment of Fertility).

Other Effects

No clinically relevant effects of pantoprazole on cardiovascular, respiratory, ophthalmic, or central nervous system function have been detected. In a clinical pharmacology study, pantoprazole 40 mg given once daily for 2 weeks had no effect on the levels of the following hormones: cortisol, testosterone, triiodothyronine (T3), thyroxine (T4), thyroid-stimulating hormone, thyroxine-binding protein, parathyroid hormone, insulin, glucagon, renin, aldosterone, follicle-stimulating hormone, luteinizing hormone, prolactin and growth hormone.

Clinical Studies

PROTONIX Delayed-Release Tablets were used in all clinical trials.

Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD)
 A US multicenter double-blind, placebo-controlled study of PROTONIX 10 mg, 20 mg or 40 mg once daily was conducted in 603 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above (Heitzel-Dart scale). In this study, approximately 25% of enrolled patients had severe EE of grade 3 and 10% had grade 4. The percentages of patients healed (per protocol, n=541) in this study were as follows:

Week	PROTONIX			Placebo
	10 mg QD (n = 153)	20 mg QD (n = 158)	40 mg QD (n = 162)	
4	45.6%*	58.4%*	75.0%**	14.3%
8	66.0%*	83.5%*	92.6%**	39.7%

(p < 0.001) PROTONIX versus placebo.
 * (p < 0.05) versus 10 mg, or 20 mg PROTONIX
 ** (p < 0.05) versus 10 mg PROTONIX

In this study, all PROTONIX treatment groups had significantly greater healing rates than the placebo group. This was true regardless of *H. pylori* status for the 20-mg and 40-mg PROTONIX treatment groups. The 40-mg dose of PROTONIX resulted in healing rates significantly greater than those found with either the 20- or 10-mg dose.

A significantly greater proportion of patients taking PROTONIX 40 mg experienced complete relief of daytime and nighttime heartburn and the absence of regurgitation starting from the first day of treatment compared with placebo. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking placebo.

PROTONIX 20 mg and 40 mg once daily were also compared with nizatidine 150 mg twice daily in a US multicenter, double-blind study of 243 patients with reflux symptoms and endoscopically diagnosed EE of grade 2 or above. The percentages of patients healed (per protocol, n=212) were as follows:

Week	PROTONIX		Nizatidine
	20 mg QD (n = 72)	40 mg QD (n = 70)	
4	61.4%*	64.0%*	22.2%
8	79.2%*	82.9%*	41.4%

(p < 0.001) PROTONIX versus nizatidine.

Once daily treatment with PROTONIX 20 or 40 mg resulted in significantly superior rates of healing at both 4 and 8 weeks compared with twice daily treatment with 150 mg of nizatidine. For the 40 mg treatment group, significantly greater healing rates compared to nizatidine were achieved regardless of the *H. pylori* status.

A significantly greater proportion of the patients in the PROTONIX treatment groups experienced complete relief of nighttime heartburn and regurgitation starting on the first day and of daytime heartburn on the second day compared with those taking nizatidine 150 mg twice daily. Patients taking PROTONIX consumed significantly fewer antacid tablets per day than those taking nizatidine.

INDICATIONS AND USAGE

Short-Term Treatment of Erosive Esophagitis Associated With Gastroesophageal Reflux Disease (GERD)

PROTONIX Delayed-Release Tablets are indicated for the short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis. For those patients who have not healed after 8 weeks of treatment, an additional 8 week course of PROTONIX may be considered.

The safety and efficacy of PROTONIX for maintenance therapy (e.g., beyond 16 weeks) have not been established. (see PRECAUTIONS).

CONTRAINDICATIONS

PROTONIX Delayed-Release Tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

PRECAUTIONS

General

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

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

Information for Patients

Patients should be cautioned that PRONIX Delayed-Release Tablets should not be split, crushed or chewed. The tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of pantoprazole.

Drug Interactions

Pantoprazole is metabolized through the cytochrome P450 system, primarily the CYP2C19 and CYP3A4 isozymes, and subsequently undergoes Phase II conjugation. Based on studies evaluating possible interactions of pantoprazole with other drugs metabolized by the cytochrome P450 system, no dosage adjustment is needed with concomitant use of the following drugs: theophylline, cisapride, antipyrine, caffeine, carbamazepine, diazepam, diclofenac, digoxin, ethanol, glyburide, an oral contraceptive (levonorgestrel/ethinyl estradiol), metoprolol, nifedipine, phenytoin, or warfarin. Clinically relevant interactions of pantoprazole with other drugs with the same metabolic pathways are not expected. Therefore, when co-administered with pantoprazole, adjustment of the dosage of pantoprazole or of such drugs may not be necessary. There was also no interaction with concomitantly administered antacids.

Because of profound and long lasting inhibition of gastric acid secretion, it is theoretically possible that pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts).

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

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

Pantoprazole was positive in the *in vitro* human lymphocyte chromosomal aberration assays, in one of two mouse micronucleus tests for clastogenic effects, and in the *in vitro* Chinese hamster ovarian cell/HGPRT forward mutation assay for mutagenic effects. Equivocal results were observed in the *in vivo* rat liver DNA covalent binding assay. Pantoprazole was negative in the *in vitro* Ames mutation assay, the *in vitro* unscheduled DNA synthesis (UDS) assay with rat hepatocytes, the *in vitro* ASS2/GPT mammalian cell-forward gene mutation assay, the *in vitro* thymidine kinase mutation test with mouse lymphoma L5178Y cells, and the *in vivo* rat bone marrow cell chromosomal aberration assay.

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

Pregnancy

Teratogenic Effects

Pregnancy Category B

Teratology studies have been performed in rats at oral doses up to 450 mg/kg/day (88 times the recommended human dose based on body surface area) and rabbits at oral doses up to 40 mg/kg/day (16 times the recommended human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to pantoprazole. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers

Pantoprazole and its metabolites are excreted in the milk of rats. It is not known whether pantoprazole is excreted in human milk. Many drugs which are excreted in human milk have a potential for serious adverse reactions in nursing infants. Based on the potential for tumorigenicity shown for pantoprazole in rodent carcinogenicity studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the benefit of the drug to the mother.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Use in Women

Erosive esophagitis healing rates in the 221 women treated with pantoprazole in US clinical trials were similar to those found in men. The incidence rates of adverse events were also similar between men and women.

Use in Elderly

Erosive esophagitis healing rates in the 107 elderly patients (≥ 65 years old) treated with pantoprazole in US clinical trials were similar to those found in patients under the age of 65. The incidence rates of adverse events and laboratory abnormalities in patients aged 65 years and older were similar to those associated with patients younger than 65 years of age. The healing rates of the 25 patients at least 75 years old were 80% for those treated with 10 mg of pantoprazole and 100% for those patients treated with either 20 or 40 mg. In addition, the safety profile in patients 65 years and older was similar to that of patients younger than 65 years of age.

ADVERSE REACTIONS

Worldwide, more than 11,100 patients have been treated with pantoprazole in clinical trials involving various dosages and duration of treatment. In general, pantoprazole has been well tolerated in both short-term and long-term trials.

In two US controlled clinical trials involving PRONIX 10-, 20-, or 40-mg doses for up to 8 weeks, there were no dose-related effects on the incidence of adverse events. The following adverse events considered by investigators to be possibly, probably or definitely related to drug occurred in 1% or more in the individual studies of GERD patients on therapy with PRONIX.

Most Frequent Adverse Events Reported as Drug Related in Short-term Domestic Trials

Study Event	% Incidence			
	Study 300-US		Study 301-US	
	PRONIX (n = 521)	Placebo (n = 82)	PRONIX (n = 161)	Nizatidine (n = 82)
Headache	6	6	9	13
Diarrhea	4	1	6	6
Flatulence	2	2	4	0
Abdominal pain	1	2	4	4
Rash	<1	0	2	0
Eruclation	1	1	0	0
Insomnia	<1	2	1	1
Hyperglycemia	1	0	<1	0

Note: Only adverse events with an incidence greater than or equal to the comparators are shown.

In addition, in these short-term domestic trials, the following treatment-emergent events, regardless of causality, occurred at a rate of ≥ 1% in PRONIX-treated patients: asthenia, back pain, chest pain, neck pain, flu syndrome, infection, pain, migraine, constipation, dyspepsia, gastroenteritis, gastrointestinal disorder, nausea, rectal disorder, vomiting, hyperlipemia, liver function tests abnormal, SGPT increased,

Prilosec® (Pantoprazole Sodium) Delayed-Release Tablets

ZES Indication

arthritis, anxiety, dizziness, hypertonia, bronchitis, cough increased, dyspnea, pharyngitis, rhinitis, sinusitis, upper respiratory tract infection, urinary frequency, and urinary tract infection.

In international short-term double-blind or open-label, clinical trials involving 20- to 80 mg per day, the following adverse events were reported to occur in 1% or more of 2805 GERD patients receiving pantoprazole for up to 8 weeks.

Study Event	% Incidence			
	Pantoprazole Total (N=2805)	Ranitidine 300 mg (N=594)	Omeprazole (N=474)	Famotidine 40 mg (N=239)
Headache	2	3	2	1
Diarrhea	2	2	2	<1
Abdominal Pain	1	1	<1	<1

Additional adverse experiences occurring in <1% of GERD patients based on pooled results from either short-term domestic or international trials are shown below within each body system. In most instances the relationship to pantoprazole was unclear.

BODY AS A WHOLE: abscess, allergic reaction, chills, cyst, face edema, fever, generalized edema, heat stroke, hernia, laboratory test abnormal, malaise, moniliasis, neoplasm, non-specified drug reaction.

CARDIOVASCULAR SYSTEM: angina pectoris, arrhythmia, cardiovascular disorder, chest pain substernal, congestive heart failure, electrocardiogram abnormal, hemorrhage, hypertension, hypotension, myocardial ischemia, palpitation, retinal vascular disorder, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation.

DIGESTIVE SYSTEM: anorexia, aphthous stomatitis, cardiospasm, colitis, dry mouth, duodenitis, dysphagia, enteritis, esophageal hemorrhage, esophagitis, gastrointestinal carcinoma, gastrointestinal hemorrhage, gastrointestinal moniliasis, gingivitis, glossitis, halitosis, hematemesis, increased appetite, melena, mouth ulceration, oral moniliasis, periodontal abscess, periodontitis, rectal hemorrhage, stomach ulcer, stomatitis, stools abnormal, tongue discoloration, ulcerative colitis.

ENDOCRINE SYSTEM: diabetes mellitus, glycosuria, goiter.

HEPATO-BILIARY SYSTEM: biliary pain, bilirubinemia, cholecystitis, cholelithiasis, cholestatic jaundice, hepatitis, alkaline phosphatase increased, gamma glutamyl transpeptidase increased, SGOT increased.

HEMIC AND LYMPHATIC SYSTEM: anemia, ecchymosis, eosinophilia, hypochromic anemia, iron deficiency anemia, leukocytosis, leukopenia, thrombocytopenia.

METABOLIC AND NUTRITIONAL: dehydration, edema, gout, peripheral edema, thirst, weight gain, weight loss.

MUSCULOSKELETAL SYSTEM: arthritis, arthralgia, bone disorder, bone pain, bursitis, joint disorder, leg cramps, neck rigidity, myalgia, tenosynovitis.

NERVOUS SYSTEM: abnormal dreams, confusion, convulsion, depression, dry mouth, dysarthria, emotional lability, hallucinations, hyperkinesia, hypesthesia, libido decreased, nervousness, neuralgia, neuritis, paresthesia, reflexes decreased, sleep disorder, somnolence, thinking abnormal, tremor, vertigo.

RESPIRATORY SYSTEM: asthma, epistaxis, hiccup, laryngitis, lung disorder, pneumonia, voice alteration.

SKIN AND APPENDAGES: acne, alopecia, contact dermatitis, dry skin, eczema, fungal dermatitis, hemorrhage, herpes simplex, herpes zoster, lichenoid dermatitis, maculopapular rash, pain, pruritus, skin disorder, skin ulcer, sweating, urticaria.

SPECIAL SENSES: abnormal vision, amblyopia, cataract specified, deafness, diplopia, ear pain, extraocular palsy, glaucoma, otitis externa, taste perversion, tinnitus.

UROGENITAL SYSTEM: albuminuria, balanitis, breast pain, cystitis, dysmenorrhea, dysuria, epididymitis, hematuria, impotence, kidney calculus, kidney pain, nocturia, prostatic disorder, pyelonephritis, scrotal edema, urethral pain, urethritis, urinary tract disorder, urination impaired, vaginitis.

Postmarketing Reports

There have been spontaneous reports of adverse events with the post-marketing use of pantoprazole. These reports include anaphylaxis; angioedema (Quincke's edema); anterior ischemic optic neuropathy; severe dermatologic reactions, including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis (TEN, some fatal); and pancreatitis.

In addition, also observed have been jaundice, confusion, hypokinesia, speech disorder, increased salivation, vertigo, nausea, and tinnitus.

Laboratory Values

In two US controlled trials, 0.4% of the patients on 40 mg pantoprazole experienced SGPT elevations of greater than three times the upper limit of normal at the final treatment visit. Except in those patients where there was a clear alternative explanation for a laboratory value change, such as intercurrent illness, the elevations tended to be mild and sporadic. The following changes in laboratory parameters were reported as adverse events: creatinine increased, hypercholesterolemia, and hyperuricemia.

OVERDOSAGE

Some reports of overdosage with pantoprazole have been received. A spontaneous report of a suicide involving an overdosage of pantoprazole (560 mg) has been received; however, the death was more reasonably attributed to the unknown doses of chloroquine and zopiclone which were also taken since two other reported cases of pantoprazole overdosage involved similar amounts of pantoprazole (400 and 600 mg) with no adverse effects observed. One patient in a flexible dosing study of refractory peptic ulcer disease received a dose of 320 mg per day for 3 months; treatment was well tolerated. Doses of up to 240 mg per day, given intravenously for seven days, have been administered to healthy subjects and have been well tolerated.

Pantoprazole is not removed by hemodialysis.

Single oral doses of pantoprazole at 709 mg/kg, 798 mg/kg and 887 mg/kg were lethal to mice, rats and dogs, respectively. The symptoms of acute toxicity were hypoactivity, ataxia, hunched sitting, limb-splay, lateral position, segregation, absence of ear reflex, and tremor.

DOSAGE AND ADMINISTRATION

Treatment of Erosive Esophagitis

The recommended adult oral dose is 40 mg given once daily for up to 8 weeks. For those patients who have not healed after 8 weeks of treatment, an additional 8-week course of PROTONIX may be considered. (See INDICATIONS AND USAGE)

No dosage adjustment is necessary in patients with renal impairment, hepatic impairment, or for elderly patients. No dosage adjustment is necessary in patients undergoing hemodialysis.

PROTONIX Delayed-Release Tablets should be swallowed whole, with or without food in the stomach. Concomitant administration of antacids does not affect the absorption of PROTONIX.

Patients should be cautioned that PROTONIX Delayed-Release Tablets should not be split, chewed or crushed.

HOW SUPPLIED

PROTONIX is supplied as 40 mg yellow oval biconvex delayed-release tablets imprinted with PROTONIX (brown ink) on one side.

They are available as follows:

- NDC 0008-0841-10 bottles of 100
- NDC 0008-0841-81 bottles of 80
- NDC 0008-0841-91 bottles of 1000
- NDC 0008-0841-99 carton of 10 Redipak® blister strips of 10 tablets each

Storage

Store PROTONIX Delayed-Release Tablets at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F). [See USP Controlled Room Temperature].

U.S. only

US Patent No. 4,758,579



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CI 6004-3

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