

Cross-Discipline Team Leader Review

Date	November 3, 2009
From	John E. Hyde, Ph.D., M.D., Clinical Team Leader, DGP
Subject	Cross-Discipline Team Leader Review
NDA/BLA #, Supplement #	NDA 22-020/S001 & S002 NDA 20-987/S036 & S037
Applicant	Wyeth/Pfizer
Date of Submission	Dated and received November 21, 2008
PDUFA Goal Date	May 21, 2009
Proprietary Name / Established (USAN) names	PROTONIX pantoprazole
Dosage forms / Strengths	NDA 20-020: For Delayed-Release Oral Suspension / 40 mg NDA 20-987: Delayed-Release Tablets / 20 mg and 40 mg
Proposed Indication	Short-term treatment of erosive esophagitis associated with GERD in pediatric patients five years and older
Recommended:	Approval of NDA 20-987/S036 & S037 and NDA 20-020/S002 (b) (4) for NDA 20-020/S001

1. Introduction

This application, received November 21, 2008, was submitted as an SE5 (new patient population) efficacy supplement to the NDA 22-020 for Protonix, which is the trade name used for several formulations of pantoprazole by Wyeth Pharmaceuticals. This submission is a response to a Pediatric Written Request, and it also was intended to address PREA commitments for NDA 22-020. (b) (4)

(b) (4) In addition, the supplement included a PLR conversion and added a Patient Information section.

NDA 22-020 is the NDA for a granule formulation of pantoprazole, but it has a combined labeling with the tablet formulation approved under NDA 20-987. Because the submission included studies and labeling changes that also involved the tablet formulation, the Applicant agreed to submit an efficacy supplement to NDA 20-987 at the Division's request. The two supplements were jointly reviewed and kept on the original time clock.

The studies provided in the application were viewed as supporting the extrapolation of efficacy in treating erosive esophagitis to the pediatric population 1 year and older, but a placebo-controlled study of symptomatic GERD in infants under one year failed to show efficacy. (b) (4)

(b) (4) During the review cycle, the Division allowed the Applicant to change the proposed

indication to short-term treatment of erosive esophagitis in pediatric patients (see Submission and Review under Section 2, below). The reviewers recommend approval for the revised proposed indication for both NDA supplements, provided changes in labeling could be agreed upon. During the review cycle, (b) (4)

During the review cycle, Wyeth was acquired by Pfizer.

This application is not for a new molecular entity. Pantoprazole was first approved in the U.S. in 2000.

Formulation nomenclature for purposes of this review:

- The currently approved and marketed granule formulation (with official dosage form designation of “for delayed-release oral suspension”), manufactured by Nycomed and provided in a 40 mg dose, will be referred to as the “**adult granules.**”
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2. Background

General Background

Treatment of Pediatric GERD and Erosive Esophagitis

See Section 2 of the Clinical Review for an overview of gastroesophageal reflux disease (GERD) in the pediatric population. The Division has taken the position that drugs can be approved for treating GERD and erosive esophagitis (EE) in pediatric age groups older than 1 year based on extrapolation of efficacy from adults and on safety and effectiveness studies (not necessarily controlled) in pediatric patients. In patients under 1 year of age there are differences in the way GERD is diagnosed, its natural history, and its clinical significance. In view of these differences, when the Pediatric Written Request for Protonix was agreed upon, it was determined that evidence of efficacy (i.e., an adequate and well-controlled study to evaluate the existence of a treatment effect) was needed for GERD in patients younger than 1 year, rather than inferring efficacy by extrapolation from adults.

Approved therapies for GERD and EE in the pediatric population are the H₂-receptor blockers ranitidine (Zantac) and famotidine (Pepcid), and four proton pump inhibitors (PPIs): lansoprazole (Prevacid), omeprazole (Prilosec), esomeprazole (Nexium), and rabeprazole (Aciphex). Famotidine is approved for neonates through 16 years, and ranitidine is approved from 1 month through 16 years. The first three PPIs named above are approved only for ages 1 year and older; Nexium and Prevacid are approved for short-term treatment of GERD and EE, while Prilosec is also approved for the maintenance of healing of EE. Aciphex is approved for

short-term treatment of GERD only in patients 12 years and older. Recently, sNDAs containing (b) (4)

Protonix

Pantoprazole is a substituted benzimidazole compound classified pharmacologically as a proton pump inhibitor. It suppresses gastric acid secretion by inhibiting H⁺/K⁺-ATPase in gastric parietal cells. Pantoprazole is protonated and converted to the active inhibitor, a sulphenamide, in the acidic compartment of the parietal cell.

Pantoprazole is market as Protonix in several formulations of the sodium salt. The oral formulations are tablet and granules. It is also available as an IV formulation.

The oral formulations of Protonix are approved in adults for:

- Short-term treatment of erosive esophagitis associated with GERD
- Maintenance of healing of erosive esophagitis
- Pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

The recommended dose is 40 mg once daily for up to eight weeks for healing EE, for those not healed after eight weeks, an additional eight weeks of treatment can be considered. The dose is 40 mg once daily for maintenance of healing of EE. For hypersecretory conditions the recommended dose is 40 mg twice daily, with dose adjusted to patient need. Protonix is available as 40 mg or 20 mg tablets or as a packet of 40 mg (adult) granules for suspension for oral administration.

The IV formulation of Protonix is approved in adults for:

- Treatment of GERD associated with a history of erosive esophagitis
- Pathological hypersecretion associated with Zollinger-Ellison syndrome.

The recommended IV dose for GERD associated with a history of EE is 40 mg once daily. The dose for hypersecretory conditions is 80 mg every 12 hours, or 80 mg every 8 hours if needed to control acid output. None of these indications for the IV formulation has been extended to the pediatric population.

The approved Protonix labeling for the oral formulation contains precautions that a response to therapy does not preclude presence of gastric malignancy, that pantoprazole was carcinogenic in rodents but the relevance to humans is unknown, that prolonged treatment may lead to vitamin B₁₂ malabsorption, and that atrophic gastritis has been seen with pantoprazole, particularly in patients who are *H. pylori* positive. Protonix is contraindicated in patients with known hypersensitivity to its components. The pregnancy category is B. The labeling does not currently include a patient instruction sheet.

See Section 2.3 of the Clinical Review by I. Chen for details of the approval history for the various Protonix formulations. In brief, the oral formulations were developed for GI indications under Wyeth's INDs 35,441 (tablets) and 68,011 (granules). Protonix tablets were first approved under NDA 20-987 on 2/2/00 for short-term treatment of erosive esophagitis (EE); maintenance of EE healing was added on 6/12/01, and use for Zollinger-Ellison syndrome (ZE) was added

4/19/02. The currently marketed adult granule formulation was approved 11/14/07 for the same indications as the tablets. (Although failing to meet PK bioequivalence criteria, clinical bioequivalence of the granules was established with a PD study of the effect on pH.) The tablets and granules have combined labeling. The most recent labeling revision was on 12/20/07 (found under NDA 20-987, but applying to both tables and granules), in which information about antiretroviral drug interactions was added. The IV formulation was developed under IND 52,132 and approved under NDA 20-988 on 3/22/01 for GERD with a history of erosive esophagitis; ZE was added on 10/19/01.

Presubmission Communications between FDA and the IND Sponsor

A Pediatric Written Request (PWR) was initially issued on December 31, 2001, to NDA 20-987, the NDA for Protonix tablets. The PWR underwent several revisions, and the last version (Amendment # 5) was issued on May 17, 2007.

A meeting was held under IND 68,011 on May 23, 2005, to discuss endpoints for the pediatric studies. The Division of Pediatric Therapeutics and the Labeling and Endpoints Division participated. General agreement was reached on the proposed endpoints, provided the Applicant made certain revisions recommended by the FDA.

On 3/3/08 the Applicant and the FDA held a pre-sNDA meeting, at which the Applicant

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The FDA said it appeared acceptable to submit the supplement to NDA 22-020 (approved adult granules) with a letter of cross-reference to NDA 20-987 (tablets).

Submission and Review

See the Regulatory Project Manager Memorandum of 10/19/09 by R. Girardet for additional details of events during the review cycle.

This application was submitted as an efficacy supplement to NDA 20-020 on November 21, 2008, and it was received on that same date. The application was electronic. It was given Priority review status with an action date of May 21, 2009, because it was a pediatric efficacy supplement submitted in response to a Pediatric Written Request. A clinical reviewer was not assigned to the application until a month into the review cycle.

During the review it was recognized that some of the studies and proposed labeling changes were applicable to the Protonix tablet formulation, which is the subject of NDA 20-987. The Applicant was approached with the need for an additional efficacy supplement for NDA 20-987 in order to include the pediatric indication and dosing recommendations relevant to the tablet formulation. The Applicant submitted an efficacy supplement on 5/12/09 for NDA 20-987 (S036), but the Division agreed to keep the new supplement on the same review clock as the supplement for NDA 22-020, and the two supplements were reviewed jointly. Labeling supplements S002 for NDA 22-020 and S037 for NDA 20-987 were generated to permit the labeling for each formulation to include information about the other, since the two NDAs have combined labeling.

In a teleconference on 6/30/09 (minutes filed 7/1/09), the Applicant was notified that the Division was faced with a difficulty in (b) (4)

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During the 6/30/09 teleconference, the Division proposed that the Applicant consider changing the proposed indication to healing of erosive esophagitis (for which both formulations had an adult indication). The Division indicated its willingness to accept such an amendment and continue the review. In a teleconference on 7/20/09 (documented in memo filed 10/8/09) between the Applicant and the Division’s Regulatory Project Manager, the Applicant decided to change the proposed pediatric indication to healing of erosive esophagitis. The Division elected to continue its review and conduct labeling negotiations based on the new proposed indication.

Review of the application also revealed that the pediatric and adult granules did not meet the pharmacokinetic criteria for bioequivalence, although the discrepancy was small. Nonetheless, the review team felt that there was adequate information to provide pediatric dosing recommendations using the adult granules if pediatric strengths of that formulation were to be made available. (b) (4)

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No Advisory Committee meeting was convened to discuss this application.

The relevant review disciplines have all written review documents. The primary review documents relied upon are the following:

- Clinical Review by I. Chen, dated 8/10/09.
- Clinical Review Addendum by I. Chen, dated 10/20/09.
- Statistical Review and Evaluation by M. Fan, dated 4/17/09.
- Pharmacology/Toxicology Review and Evaluation by Y. Ng, dated 5/22/09.

Office of Clinical Pharmacology Review by I. Kim, J. Earp, and L. Zhang, dated 8/13/09.
Chemist’s Review by S. Kelly, dated 6/25/09.
Chemist’s Review (labels) by S. Kelly, dated 9/1/09.
RPM Labeling Review (PLR) by R. Girardet, dated 8/10/09.
RPM Memorandum by R. Girardet, dated 10/19/09.
SEALD Study Endpoint Review by P. Miskala, dated 4/3/09.
SEALD Labeling Review by A. Olagundoye, dated 4/30/09.
PMHS Labeling Review by A. Karesh, dated 5/12/09.
Pediatric Exclusivity Board Minutes of 2/13/09, dated 3/24/09
DMEPA Label and Labeling Review by R. Brown, dated 4/20/09.
DRISK Review of Patient Labeling by L. Ford, dated 5/27/09.
DDMAC Labeling Comments by K. Klemm and S. Doshi, dated 5/12/09.

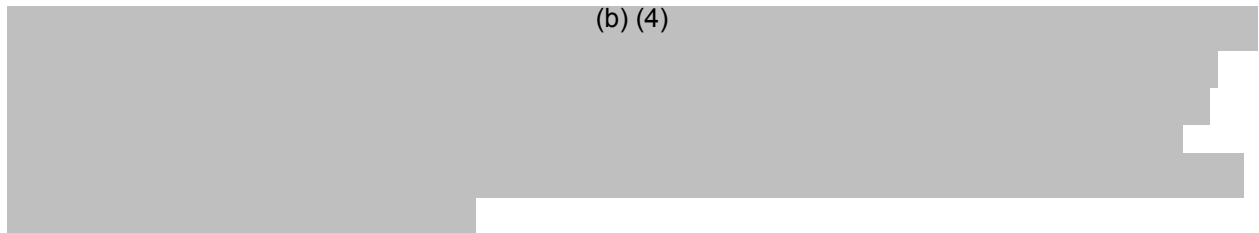
This CDTL memorandum summarizes selected information from the primary review documents. The reviews should be consulted for more specific details of the application and review conclusions.

On October 15, 2009, Wyeth, the original Applicant, became a subsidiary of Pfizer, but the Wyeth subsidiary continued to be the unit having responsibility for the application.

3. CMC

See the Chemistry Review by S. Kelly for complete information.

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4. Nonclinical Pharmacology/Toxicology

See the Pharmacology/Toxicology Review and Evaluation by Y. Ng for complete information.

Eight new studies in non-adult rats and dogs were reviewed for this supplemental application; six had already been submitted and reviewed under IND 35,441. The studies were the following:

Juvenile Rats

- 25-day repeated oral dose ranging
- 2-month oral toxicity
- 4-week toxicity with 3-month recovery in neonatal/juvenile rats
- 15-day repeated IV dose ranging
- 15-day IV toxicity

Neonatal Dogs

- 1-week oral toxicokinetics
- 13-week oral tolerability
- 13-week oral toxicity with 13-week recovery

The reviewer found that the stomach mucosa was the common target of toxicity, and increased stomach weights were seen in both species. Eosinophilic chief cells were seen in juvenile rats in all treatment groups; the changes were reversible after a three-month recovery. The findings in neonatal dogs were increased mucosal height, parietal cell hyperplasia, chief cell atrophy, mononuclear infiltrate, glandular dilation, and glandular necrosis. The inflammation and necrosis in dogs were seen at all doses. Changes in the dogs were not completely reversed after three months. Both species showed decreased hemoglobin and hematocrit, and dogs had a reversible increase in cholesterol and triglyceride. No effect on development or growth was seen in either species. Plasma exposures were seen to be higher in younger dog pups than more mature ones. The reviewer concluded that the tolerated dose was 5 mg/kg/day in rats and 3 mg/kg/day in dogs.

The Reviewer had several recommendations regarding changing the location of items for the conversion to PLR labeling format. He objected to the deletion of a paragraph describing non-clinical data in the OVERDOSAGE section, and he recommend that the carcinogenicity studies be presented individually as in currently approved labeling. In the section presenting the juvenile non-clinical results, he recommended that a statement about (b) (4) be clarified, and he recommended deletion of a statement regarding (b) (4) that he felt was not supported. (See the review for detailed labeling comments.)

Conclusions and Recommendations

The Reviewer concluded that the study results showed the toxicity profile in the juvenile and neonatal animals was similar to that seen in the adult animals. However, he noted that necrosis of stomach glands had not been seen in adult dogs, and felt the effects of pantoprazole on the neonatal dog stomach appeared more severe than the effects in adult animals.

The Reviewer recommended that, from the nonclinical perspective, the supplement could be approved, provided the labeling was revised as recommended. The Reviewer did not recommend any new Phase 4 commitments.

5. Clinical Pharmacology/Biopharmaceutics

See the Office of Clinical Pharmacology Review by I. Kim, J. Earp, and L. Zhang for complete information.

General clinical pharmacology/biopharmaceutics.

The primary Clinical Pharmacology review covered four PK or PK/PD studies: a PK/PD study in neonates and preterm infants, a PK/PD study in patients 1 through 11 months, a PK study in patients 1 through 11 years, and a PK study in patients 12 through 16 years.

Key PK findings in patients 1 year and older are shown in the table below (from Tables 2 and 3 in the Clinical Pharmacology review):

Age in years Dose	1 to 5 1.2 mg/kg	6 to 11 40 mg tab	12 to 16 40 mg tab
C _{max} (µg/mL)	0.7	3.3	1.8
T _{max} (h)	1.7	1.3	1.5
AUC (µg•h/mL)	5.4	6.9	5.5
Cl/F (L/h)	3.1	6.6	6.8

From current labeling, the corresponding PK parameters for adults administered a 40 mg tablet are C_{max} of 2.5 µg/mL, T_{max} of 2.5 h, and AUC of 4.8 µg•h/mL.

Note: In the course of labeling negotiations after the Clinical Pharmacology Review was completed, the Clinical Pharmacology review team revised their estimates of the pediatric PK parameters. Therefore, some of the values appearing in the final recommended labeling differ from those in the Clinical Pharmacology Review.

A PK bioequivalence comparison of the pediatric granules and the 40 mg tablet showed lower exposure from the pediatric granules (given with applesauce) compared to the tablet (from Table 4 in the Clinical Pharmacology Review):

BE Comparison of Pediatric Granules to Approved 40 mg Tablet*

	C _{max}	AUC
Ratio of means	62%	90%
90% C.I.	56% - 70%	85% - 96%

*Ratios shown are pediatric granule PK parameter over tablet PK parameter

A PK bioequivalence study in adults comparing the adult and pediatric granules gave the following results showing somewhat higher exposures from the adult granules (from Table 5 in the Clinical Pharmacology review):

BE Comparison of Adult Granules to Pediatric Granules*

	Cmax	AUC
Ratio of means	118%	106%
90% C.I.	108% - 129%	100% - 113%

*Ratios shown are adult granule PK parameter over pediatric granule PK parameter

CDTL Reviewer Comment:

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In a PD study of 16 preterm infants and neonates, a 2.5 mg daily dose of Protonix given for at least five days produced increases in intragastric pH and in the % time intragastric pH was > 4. Intra-esophageal pH changes were not statistically significant; in fact, the mean intra-esophageal pH showed a decreasing trend. In a second PD study, infants ages 1 to 11 months were given at least five day's treatment with either 0.6 mg/kg (n=11) or 1.2 mg/kg (n=10) of Protonix daily. Treatment produced significant changes in intragastric pH only at the higher dose (but the low dose group was more than 1 pH unit higher at baseline). Mean intra-esophageal pH tended to decrease rather than increase, and neither dose produced a significant change in % time intra-esophageal pH was < 4.

Drug-drug interactions

Drug-drug interaction information is present in current labeling. No additional drug-drug interaction studies were presented in this supplement.

Pharmacogenomics

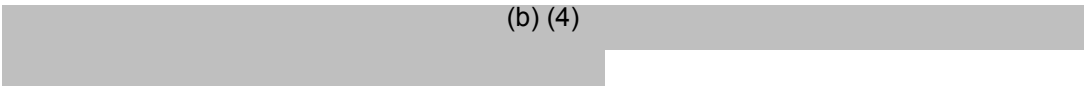
There were six genotyped pediatric patients who had the poor metabolizer genotype of CYP 2C19. Pediatric poor metabolizers had greater than six-fold higher AUCs for pantoprazole.

Demographic interactions/intrinsic factors/special populations

A population PK analysis was undertaken by the Applicant as described in the Pharmacometrics Review section of the Clinical Pharmacology Review. Age, weight, and CYP2C19 metabolizer status were found to be important factors. The effects of race and gender were small and felt to be not critical for dosing recommendations.

Conclusions and Recommendations

The Clinical Pharmacology Reviewers drew the following conclusions regarding the pharmacokinetic and pharmacodynamic information in the submission:

- Body weight is the key covariate factor affecting pantoprazole clearance in patients older than 3 years, whereas age had a significant influence on clearance in patients less than 1 year of age.
- Plasma concentrations in children were highly variable, with CVs of about 90%, and some patients had no measureable pantoprazole concentrations.
- Administration of 0.6 mg/kg (approximate adult equivalent) to infants through 11 years provided lower systemic exposure than administering a 40 mg tablet dose to adults.
- Administering 1.2 mg/kg to patients 1 to 5 years produced AUCs about 37% higher than adults receiving a 40 mg tablet
- Administering the 40 mg tablet to pediatric patients produced AUCs 39% higher than adults in patients 6 to 11 years, and 10% higher in patients 12 to 16 years.
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The Clinical Pharmacology Reviewers found the clinical pharmacology and biopharmaceutics information in the supplemental NDA acceptable from the Clinical Pharmacology perspective, provided the dosing recommendations were modified to include adjustments based on weight so that pediatric exposures better matched adult exposures, and provided agreement could be reached on labeling. They also recommended that labeling include the advice to use a lower dose in pediatric patients known to have the poor metabolizer genotype of CYP 2C19. The Reviewers did not recommend any new Phase 4 commitments.

6. Clinical Microbiology

Clinical Microbiology considerations do not apply to these supplements because Protonix does not have an antimicrobial indication.

7. Clinical/Statistical – Efficacy

The reader is referred to the Clinical Review by I. Chen and the Statistical Review by M. Fan for complete information. See also the Clinical Review Addendum by I. Chen.

This submission contained one placebo-controlled efficacy study in infants and three dose-ranging studies in different age ranges for children from 1 year to 16 years. These studies represented the clinical safety and effectiveness trials submitted in response to the Pediatric Written Request.

Infant Efficacy Study – Study 329

This study was a randomized, double-blind, placebo-controlled, multicenter, treatment-withdrawal study in infants with GERD. There were 31 actively participating sites in seven countries; 18 centers were in the U.S. The study enrolled 129 patients, of whom 108 continued to the treatment-withdrawal phase. In the four-week treatment-withdrawal phase, patients were randomized to placebo or Protonix using weight-based dosing. Efficacy was assessed by comparing proportions of patients who withdrew due to worsening disease.

Eligibility, treatment, and assessments

To be eligible, patients needed to be at least 1 month but less than 12 months old. Pre-term infants needed to have a corrected gestational age of at least 44 weeks. Weight was required to be between 2.5 and 15 kg. Patients needed to have a diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, the diagnosis being made by the investigator based on assessment of history, physical, symptoms, or diagnostic testing. At least one symptom had to be present at least twice a week for four weeks. Patients also needed to have a mean symptom frequency > 16 on the GERD Symptom Questionnaire for Infants (GSQ-I). Patients were excluded for upper GI anatomic or motor disorders, history of life-threatening GERD manifestations, use of PPI or H2 blockers within 14 days, or significant medical conditions. See the Clinical Review for details of the eligibility criteria.

All enrolled patients were treated initially with standardized, non-pharmacologic treatment for two weeks. Patients whose symptoms did not improve were then treated with Protonix pediatric granules for four weeks in an open-label phase. The dosing was based on weight in two weight ranges targeting an approximate dose of 1.2 mg/kg: patients 2.5 kg to < 7 kg were dosed 5 mg once daily; patients 7 kg through 15 kg were dose 10 mg once daily. A liquid antacid was provided for use as rescue medication, but other GERD treatments were prohibited.

After four weeks of run-in treatment, patients for whom the investigator confirmed a clinical response, and who were 80% compliant with medication and diary completion, were randomized 1:1 to receive placebo or continue receiving Protonix for a subsequent four-week, blinded, treatment-withdrawal phase. Patients were allowed to continue using liquid antacid up to 35 mg/kg/day as rescue medication.

During the treatment-withdrawal phase, patients who showed lack of efficacy were to be discontinued from treatment. Lack of efficacy was defined as any of: GERD symptom frequency returning to the baseline rate or above for two consecutive weeks, worsening on

endoscopy if performed, maximal antacid use for seven consecutive days, severe GERD symptoms based on physician's judgment, or investigator's determination that patients should be withdrawn for lack of efficacy.

In-office study visits were conducted every two weeks from the start of the open-label phase through the end of the treatment withdrawal phase. Telephone contacts were made in the intervening weeks and at two weeks after completing treatment. An eDiary was used to collect information on various GERD symptoms using a Caregiver Assessment of GERD Symptoms for Infants (CAGS-I) questionnaire. A Weekly GERD Symptom Score (WGSS) was calculated based on selected items from the CAGS-I.

Endpoints

The primary endpoint was the proportion of patients withdrawing due to worsening of symptoms, to be compared with Fisher's exact test.

Protocol-specified major secondary analyses were: 1) proportion withdrawing for any cause, 2) time to withdrawal, 3) mean frequency of GERD symptoms, 4) antacid use, and 5) frequency of respiratory symptoms.

Results

From 154 patients screened, 129 patients from 31 centers were enrolled in the open-label phase of Study 329. Of these, 108 continued into the randomized treatment-withdrawal phase with 54 patients in each arm. However, of the patients assigned to Protonix, one was given double-blind treatment in the open-label phase and one had eosinophilic esophagitis, leaving a total of 106 patients in the mITT population, with only 52 in the Protonix arm. Among mITT patients in the treatment-withdrawal phase, the mean age was 5.1 months, the mean weight was 7.0 kg, percent male was 64%, percent Caucasian was 66%.

Prior to the final visit, 12 patients, 6 in each arm, discontinued during the treatment-withdrawal phase due to lack of efficacy. This produced discontinuation rates of 11% for placebo and 12% for Protonix ($p = 1.00$). The Kaplan-Meier curves for the two arms appeared similar and other sensitivity analysis of the primary endpoint also showed essentially no difference between treatment arms (see Statistical Review for additional details).

During the initial, open-label phase, the WGSS improved, as did the frequency of the five individual GERD symptoms. However, there was no relapse of symptoms in the placebo group at the end of the double-blind phase, and there was no consistent difference in symptoms between arms in double blind phase.

The Statistical Reviewer concluded there was no difference between treatment groups in withdrawal rates due to lack of efficacy. The Clinical Reviewer concluded there was not convincing evidence to support use of PPI in this age group.

1 through 5 Years Clinical Outcome and Safety Study – Study 328

This study was a randomized, double-blind, multicenter study comparing three doses of Protonix for eight weeks in 60 patients ages 1 through 5 years with endoscopically proven symptomatic GERD. There was no placebo control. Effectiveness was evaluated by symptom scores.

Eligibility, treatment, and assessments

Patients needed to be 1 through 5 years old with weight > 7.0 kg, and with a diagnosis of GERD confirmed within two weeks of enrollment by either: 1) endoscopic evidence of reflux-related erosive esophagitis (EE), or 2) histological evidence of esophagitis consistent with GERD (and excluding eosinophilic esophagitis). Patients needed to have a GERD symptom frequency score > 3 on the GERD Symptom Questionnaire-Young Child (GSQ-YC). Exclusion criteria were similar to those used in Study 329, above. See the Clinical Review for details.

Three dose groups were defined: low (5 mg once daily, targeting 0.3 mg/kg/day), medium (10 mg once daily, targeting 0.6 mg/kg/day), and high (15 or 20 mg once daily depending on age, targeting 1.2 mg/kg/day); dosing was in the form of pediatric granules administered with applesauce or apple juice. Patients without EE were randomly assigned with equal probability to one of the three doses. Patients with EE were randomly assigned with equal probability to only the medium and high doses. The assigned treatment was administered for eight weeks. Liquid antacid was provided as rescue for GERD symptoms, not to exceed 35 mg/kg/day; other medications to treat GERD were not permitted.

In-office study visits were conducted at every two weeks during treatment. There was telephone contact on the intervening weeks and two weeks after completion of treatment. Office visit evaluations included physical exams, adverse events, growth parameters, ECG, and laboratory tests. GERD symptoms were collected from parents or caregivers using an eDiary based on the GSQ-YC and I-GERD questionnaire, and a Weekly GERD Symptom Score (WGSS) was calculated based on five selected symptoms. Use of rescue and other concomitant medications was recorded. Patients with EE at baseline had repeat endoscopy at the end of the treatment period.

Endpoints

The primary endpoint was the WGSS, defined as the sum of GERD symptoms scores for vomiting/regurgitation, choking/gagging, refusal to eat, difficulty swallowing, and abdominal/belly pain (see Clinical Review for details of the questionnaire and scoring system).

Protocol-specified major secondary endpoints were: 1) individual mean frequency score for each symptom, 2) amount of antacid used and number of patients using antacids, 3) individual respiratory symptom scores, 4) change in endoscopy results, and 5) healing of EE among those having EE at baseline.

Results

From 101 patients screened at 26 sites in North America, 60 patients were randomized to treatment in Study 328. The mean age was 2.4 years, the mean weight was 15 kg, percent male was 62%, and percent Caucasian was 83%. Four patients had EE at baseline (defined as a Hetzel-Dent endoscopy score ≥ 2), with two each in the medium and high dose arms.

The mean WGSS decreased statistically significantly from baseline to Week 8 in the low and high dose groups, but not in the medium dose group. The medium dose group had lower baseline scores, younger patients, and more males than the other two groups. Scores for individual symptoms decreased over the treatment period in all dose groups, but only improvement in abdominal pain was statistically significant for all three groups, and there was

no statistically significant difference between the dose groups. There were trends toward reductions in antacid use and respiratory symptoms. The Clinical Reviewer also noticed that there appeared to be a nominally statistically significant correlation between Protonix dose and Miralax use.

Of the four patients with erosive esophagitis, two were assigned the medium dose and two were assigned the high dose. All four had healing of EE at the end of treatment (defined as Hetzel-Dent score ≤ 1).

The Clinical Reviewer agreed with the findings of healing of EE and concluded that the results supported the use of Protonix for short-term treatment of EE in patients 1 to 5 years. She concluded that none of the secondary endpoints supported additional labeling claims.

Because this study was not designed or sized to have the potential to provide substantial evidence of efficacy, it did not receive a detailed statistical review.

5 through 11 Years Clinical Outcome and Safety Study – Study 322

This study was a randomized, double-blind, multicenter study comparing daily doses of 10 mg, 20 mg, or 40 mg Protonix for eight weeks in 53 randomized patients ages 5 through 11 years with endoscopically confirmed symptomatic GERD. There was no placebo control. Effectiveness was evaluated using symptom scores.

Eligibility, treatment, and assessments

Patients needed to be ages 5 through 11 years old, with weight ≥ 20 kg and at or above the 10th percentile. Patients had to have a diagnosis of GERD confirmed by endoscopic or histologic evidence within two weeks of enrollment, or by pH-metry within 90 days of enrollment showing esophageal pH < 4 for $\geq 6\%$ of the time. Patients were also required to have a score of ≥ 16 on the GERD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q, see Clinical Review for description of this questionnaire). Exclusion criteria were similar to those for Study 329, above.

Patients were randomized with equal probability to receive pantoprazole enteric-coated tablets 10 mg, 20 mg, or 40 mg once daily for eight weeks. Patients were allowed to have study-provided antacid as rescue medication, but other GERD treatments were prohibited.

In-office study visits were conducted every two weeks during treatment. There was telephone contact on the intervening weeks and two weeks after completion of treatment. Office visit evaluation consisted of a brief physical exam and adverse events; labs were performed at Week 4. GERD signs and symptoms were collected using the GASP-Q questionnaire. Use of rescue medication and other concomitant medications was recorded. Repeat endoscopy at the end of the study was obtained for patients who had pathological findings on the baseline endoscopy.

Endpoints

The primary endpoint was the change in the Composite Symptom Score (CSS), which was the sum of individual symptoms scores obtained by multiplying frequency and severity of symptoms recorded on the GASP-Q questionnaire.

Protocol-specified major secondary endpoints were: 1) changes in Individual Symptoms Scores (ISS) from the GASP-Q, 2) need for antacids, 3) physician's global assessment at the final visit. Other endpoints included assessment of healing of erosive esophagitis (EE).

Results

From 76 patients screened at 18 U.S. sites, 53 were randomized in Study 322. Among those randomized, the mean age was 8.1 years, the median weight was 33 kg, percent male was 36%, and percent Caucasian was 58%. All of the patients satisfied eligibility criteria by having endoscopy within two weeks of enrollment; none was enrolled based on pH-metry criteria. Four patients had EE at baseline (defined as a Hetzel-Dent endoscopy score ≥ 2); three received the 20 mg dose, and one received 40 mg.

All dose groups showed statistically significant changes from baseline in CSS: the mean scores ranged from 129 to 135 across the groups at baseline, and they had decreased to a range of 28 to 43 across the groups at Week 8 (see Clinical Review for details). There were no statistically significant differences between the three dose groups for change in CSS at Week 8, although an analysis of time to improvement indicated that improvement in CSS was slower in the 10 mg dose group. Most of the patients with non-erosive esophagitis showed endoscopic improvement; but there were also no differences between dose groups.

Of the four patients with EE at baseline, all showed endoscopic healing (Hetzel-Dent score ≤ 1) at Week 8, and two had at score of 0 (normal).

The Clinical Reviewer concluded that all dose groups showed improvement in GERD symptoms, but that improvement by Week 1 was better for the 20 mg and 40 mg dose groups. She concluded that all four patients with EE had endoscopic healing by the end of the trial, and that the data supported extrapolation of efficacy from the adult population to patients 5 to 11 years.

Because this study was not designed or sized to have the potential to provide substantial evidence of efficacy, it did not receive a detailed statistical review.

12 through 16 Years Clinical Outcome and Safety Study – Study 326

This study was a randomized, double-blind, multicenter study comparing daily doses of 20 mg or 40 mg Protonix for eight weeks in 136 patients ages 12 through 16 years with symptomatic GERD. There was no placebo control. Effectiveness was evaluated using symptom scores.

Eligibility, treatment, and assessments

Patients needed to be ages 12 through 16, with weight at least at the 5th percentile, and with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD. Endoscopy was not needed to qualify for eligibility. Patients were required to have a Composite Symptom Score (CSS) of at least 16 based on the GERD Assessment of Symptoms in Pediatrics Questionnaire (GASP-Q). Exclusion criteria were similar to those for Study 329, above.

Patients were randomized with equal probability to receive Protonix 20 mg or 40 mg once daily for eight weeks. Patients were allowed to have study-provided antacid as rescue medication, but other GERD treatments were prohibited.

In-office study visits were conducted every two weeks during treatment. There was telephone contact on the intervening weeks and at two weeks after completion of treatment. Office visit evaluation consisted of a brief physical exam and adverse events; labs were performed at Week 4. GERD signs and symptoms were collected using the GASP-Q questionnaire. Use of rescue medication and other concomitant medications was recorded. There was no requirement for endoscopy at the end of the study.

Endpoints

As in Study 322, above, the primary endpoint was change in CSS score from baseline to Week 8.

Protocol-specified secondary endpoints included six additional endpoints based on various symptom assessments, antacid use, and physician's global assessment.

Results

From 159 patients screened, 136 were enrolled from 24 active sites. Only three patients had endoscopy during screening visits. Among those randomized, the mean age was 14 years, the median weight was 61 kg, percent male was 32%, and percent Caucasian was 77%.

The CSS fell from 178 at baseline to 67 at Week 8 in the group receiving 20 mg Protonix, and from 174 at baseline to 58 at Week 8 in the group receiving 40 mg. The changes from baseline were highly statistically significant, but there was no statistically significant difference between the two dose groups.

The individual symptom scores improved, primarily due to decreasing frequency rather than decreased severity. Physician's global assessments also were improved at Week 8 compared to baseline. Antacid use decreased slightly at the end of the trial but there was no difference between dose groups in antacid use.

The Clinical Reviewer concluded that this study showed improvement in symptoms. Because no patient in this study had a diagnosis of EE, she drew no specific conclusions about the effect of Protonix on EE from this study.

Because this study was not designed or sized to have the potential to provide substantial evidence of efficacy, it did not receive a detailed statistical review.

Consults

Study Endpoint and Label Development (SEALD)

SEALD was consulted early in the review cycle regarding the endpoint questionnaires used in the studies described above. The SEALD Reviewer noted there were prior agreements about pediatric endpoints in a meeting with the Applicant on 5/23/05 under IND 68,011. The Reviewer felt that the Applicant had not provided adequate empirical evidence of content validity for the various clinical outcome instruments (GSQ-I, GSQ-YC, and GASP-Q) and that there was no responder definition to help understand what would constitute a clinically meaningful change in each instrument. The Reviewer also noted that the submission did not include information on the translation and adaption for the GSQ-I (infant questionnaire) for other countries, and she recommended analysis by country. She also noted that the GASP-Q used a

proxy assessment for ages 5 through 11, and could have involved proxy assessment for ages 12 through 16.

The Reviewer recommended careful evaluation of data across studies to make sure findings were consistent for the different instruments, and she recommended evaluation of each behavior/symptom to make sure treatment did not produce any meaningful decrements. For labeling, the Reviewer recommending against using the term “composite symptom score” to describe the endpoints because it was not an accurate description of what was measured. She also recommended that any reporting of the results in labeling should disclose deficiencies in the measures used in patients 5 through 16 years.

Integrated Analysis of Effectiveness in Erosive Esophagitis

In Studies 328 and 322, which spanned the age range 1 year to 11 years, there were eight patients with erosive esophagitis (EE), four in each study. In the younger age range (1 to 5 years), two patients were dosed with 10 mg Protonix, and two patients received 20 mg. In the older age range (6 to 11 years), three received 20 mg, and one receive 40 mg. All eight patients had healing of erosions after eight weeks of treatment. The estimated healing proportion is 100%, with a 97.5% lower confidence bound of a 37% healing proportion.

Clinical/Statistical Efficacy Conclusions and Recommendations

The Statistical Reviewer concluded that Study 329 (the infant study) showed no treatment difference between groups. While he proposed that lack of treatment effect was the likely cause for the result, he allowed that sample size could have been a factor.

The Clinical Reviewer concluded that if efficacy is extrapolated from the established adult erosive esophagitis indication, the available pediatric data in the submission could support the same indication of short-term treatment of EE associated with GERD, and she recommended approval of Protonix for healing of EE for pediatric patients 1 year an older. (b) (4)

she recommended that the indication be modified to healing of EE in pediatric patients 5 years and older (see Clinical Review Addendum, dated 10/20/09).

(b) (4)

The Clinical Reviewer recommended that PREA commitment #1 for NDA 22-020, to study treatment of EE in patients birth to 17 years, be considered fulfilled. She felt that the Applicant’s literature review of pediatric PPI use was not an adequate response to PREA commitment #2 for NDA 22-020, which called for a study of maintenance of healing of EE.

(b) (4)



8. Safety

In addition to safety data from the four studies described in the Clinical/Statistical Section above, the Applicant also provided safety data from the four PK and PK/PD studies that were conducted as part of the Pediatric Written Request and from four additional studies of oral and IV pantoprazole that were conducted apart from the Written Request. The latter four had no concerning safety signals, and the clinical safety review focused on the eight studies related to the Written Request. The only placebo-controlled safety data came from the infant study (Study 329).

There were no deaths in the clinical studies. (However, there was a death a patient receiving IV Protonix in one of the IV studies. The death was considered a complication of a traumatic injury predating treatment and not related to study drug.) There were 23 patients reporting serious adverse events (SAEs), none was considered related to treatment. The type of SAE varied widely, with the most common event being viral gastroenteritis in three patients.

In the infant study (Study 329), one patient had new QTc prolongation at the end of the open-label run-in, and at the end of the treatment-withdrawal phase there were two new QTc prolongations each in the placebo and Protonix arms. The Clinical Reviewer noted that QTc abnormalities were not uncommon, being present in 8.5% of patients at screening, and that QTc interpretation in infants can be difficult. The study ECG reader did not report any ECGs as showing a “clinical significant abnormality.” Potentially clinically important ECG changes were not seen in the other age groups. The Clinical Reviewer concluded that the findings did not represent a signal for a QT prolongation effect.

The Clinical Reviewer conducted her own review of common adverse events (AEs) after reassignment of preferred terms in the combined safety data. The most commonly reported AEs (> 4%) in the pediatric population 1 year and older were URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain. In the infant study, the most common AEs (and > 4% more than placebo) were elevated CK, otitis media, rhinitis, and laryngitis. The Clinical Reviewer noted that several patients in the infant study had CK elevations at baseline, that the CK elevations that developed after starting Protonix therapy were not to a level considered potentially clinically significant, and that mean CK levels were similar for the treatment groups. She concluded that the data did not indicate that pantoprazole presented a major risk for CK elevation in infants.

The Clinical Reviewer concluded that a detailed table of common adverse events specific for the pediatric trials did not need to appear in the labeling because the adverse reactions described for adults in the labeling are relevant for pediatric patients.

Safety Conclusions and Recommendations

The Clinical Reviewer concluded that there was sufficient evidence of safety to support approval, and she made recommendations for AE labeling as described above.

9. Advisory Committee Meeting

This application was not presented to an Advisory Committee.

10. Pediatrics

Exclusivity

The submission was presented to the Pediatric Exclusivity Board on 2/13/09. Pediatric Exclusivity was granted, effective 2/17/09, and a notification was faxed to the Applicant on 2/18/09.

PeRC

The application was presented to the Pediatric Research Committee (PeRC) on 4/22/09. The Committee recommended that the lack of effectiveness in patients younger than 1 year be clearly stated in the labeling and that the study results and pertinent pharmacokinetic information for that age group be included in the pediatric section of labeling.

PREA

The initial Approval Letter for NDA 22-020, dated 11/14/07, contained the following pediatric study requirements:

1. Deferred pediatric study under PREA for the treatment of erosive esophagitis associated with gastroesophageal reflux disease in pediatric patients ages birth to seventeen years.

Final Report Submission: December 31, 2008

2. Deferred pediatric study under PREA for the maintenance of healing of erosive esophagitis in pediatric patients ages birth to seventeen years.

Final Report Submission: December 31, 2008

There are no outstanding PREA commitments for NDA 20-987.

The studies in this supplement constitute a response to PREA commitment #1 as well as to the Pediatric Written Request. Although these studies generally satisfy that commitment, the infant study (Study 329) was technically deficient in meeting the letter of the commitment because it did not include patients from birth to 1 month. Given the practical limitations of the time needed

to make a diagnosis and attempt non-pharmacologic intervention, it would be reasonable for the Division to consider it unnecessary and impractical to study the particular age group of patients less than 1 month of age for treatment of erosive esophagitis, and to consider the commitment fulfilled, as the Clinical Reviewer recommended

PREA commitment #2 was not addressed directly in this submission, because only short-term treatment was evaluated. The Applicant provided a review of the literature on pediatric PPI use that included some longer-term treatment (see section 9.1 of the Clinical Review), but the Clinical Reviewer did not feel that the data in the application supported an indication beyond short-term treatment for healing of erosive esophagitis. Commitment #2 should not be considered fulfilled.

11. Other Relevant Regulatory Issues

Standard of Evidence for Efficacy for GERD

Although extrapolation of efficacy from adults formed part of the basis for the approval of other PPIs for treating GERD in pediatric patients over 1 year of age, differences in the nature of the disease in patients under 1 year has led to the position, as reflected in the Pediatric Written Request, that efficacy cannot be extrapolated to the latter age group, and independent evidence of efficacy is necessary. See Sections 1 and 2 the Clinical Review for additional discussion of this issue. The efficacy study presented in this submission (Study 329) failed to provide substantial evidence of efficacy in pediatric GERD for patients less than 1 year. Because the evidence of efficacy is lacking, this Reviewer agrees with the Statistical and Clinical Reviewers that an indication for Protonix for GERD in patients less than 1 year not be approved.

(b) (4)



Evidence of Efficacy for EE

Both the approved tablet and (adult) granule formulations have an indication for the healing of erosive esophagitis; the granule formulation indication was based on the demonstration of clinical bioequivalence of the 40 mg granules to the 40 mg tablets. The Division has taken the position that there is sufficient similarity between adult EE and EE in patients 1 year and older that extrapolation of efficacy from adults to children can form part of the basis for a pediatric indication.

The evidence of effectiveness of Protonix tablets for healing of EE (4 of 4 healed) in children ages 5 through 11 years in Study 322, the evidence of safety in children ages 5 through 16 years in Studies 322 and 326, together with extrapolation from adults, provides an adequate basis for

extending the EE healing indication for Protonix tablets to children 5 through 16 years. Although EE healing was not assessed in the study of patients 12 through 16 years, given that extrapolation of efficacy to a younger age range is accepted, then *interpolation* of efficacy to this age range is acceptable as well. Study 328, which provided data on effectiveness in patients 1 through 5 years using the pediatric granules, also provides some general support for the indication (but it should be noted that the pediatric granules are not bioequivalent to the tablets).

(b) (4)



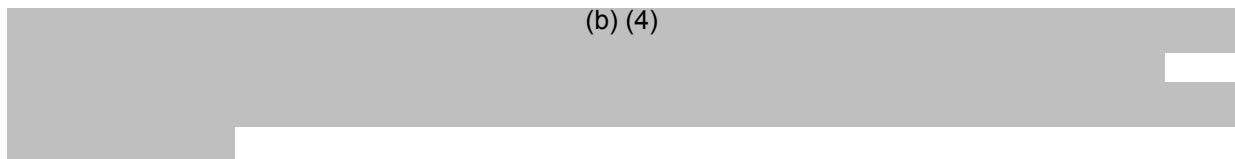
Exclusivity

Pediatric exclusivity as a result of fulfilling a Written Request was granted by the Pediatric Exclusivity Board on 2/17/09. (b) (4)



For NDA 20-987/S036 (the tablet efficacy supplement), Study 322, which provided effectiveness and safety data for the tablets in children 5 through 11 years, and Study 326, which provided safety data for the tablets in patients 12 through 16 years, are new studies that can be considered essential to the approval. Study 328, which provided effectiveness and safety data for the pediatric granules in children 1 through 5 years, provided supporting information, but in view of the facts that: 1) it did not use the tablet formulation, 2) it was not done in an age range for which the tablets are being indicated, and 3) pediatric effectiveness data in EE were also provided from another study (Study 322), it is reasonable to say that Study 328 is not *essential* to the approval of the tablet efficacy supplement. As a corollary, Study 328 is also not essential to the approval of an indication for the adult granules for healing of EE in pediatric patients who should take a 40 mg dose, because that indication is a consequence of the clinical bioequivalence previously established between the 40 mg tablet and 40 mg adult granule dose.

(b) (4)



Division of Scientific Investigations (DSI) Audits

Clinical site inspections were conducted for two investigators: P. Bishop in Jackson, MS, and M. Tsou in Norfolk, VA. Each site participated in both Study 322 and Study 328. The DSI Reviewer recommended that the data generated by the clinical sites appeared acceptable in support of the application.

12. Labeling

These sNDAs also included conversion to PLR labeling format and added a new Patient Information section.

Labeling Consults

The Division of Drug Marketing, Advertising, and Communications (DDMAC) made several recommendations regarding labeling; many involved changes to currently approved sections to reduce potential for misinterpretation or to improve compliance with current labeling practice. Refer to the DDMAC labeling review for details. The review team decided to adopt several of the recommendations, but the team felt that the precedent of the currently approved labeling wording precluded implementing some of the recommendations.

The Study Endpoints and Label Development (SEALD) team reviewed the labeling and made several suggestions to improve compliance with PLR requirements.

The Division of Risk Management (DRISK) reviewed the new Patient Information section of the labeling and made several recommendations to simplify the wording, improve clarity, remove redundancy, and ensure consistency with the package insert.

The Division of Medication Error Prevention and Analysis (DMEPA) reviewed the carton and container labels. (b) (4)

They also recommended changing the wording to take “additional sips of water” to wash down granules, because it created a misleading impression that water could be used for the initial administration.

Specific Labeling Issues

(b) (4)

, and final labeling was agreed upon. The following points were considerations in arriving at a final recommended labeling:

- Because Study 329 (GERD in patients younger than 1 year) was conducted in response to a Pediatric Written Request, but did not support a change in indications or dosing recommendations for the pediatric population, the study should be reported in labeling, but it should be included only in Section 8.4, Pediatric Use, rather than in Section 14, Clinical Studies.
- Because the studies in patients 1 year and older were conducted in response to a Pediatric Written Request, the results also needed to be reflected in labeling. The findings in the subset of patients with EE in Study 322 (ages 5 through 11 years) are appropriate to include in Section 14, Clinical Studies, because they support the expansion of the indications. The findings for patients with EE in Study 328 (ages 1 through 5 years) should be reported in Section 8.4, which should also include an explanation (lack of age-appropriate formulation) for why the indication does not include patients younger than 5 years despite a finding of effectiveness.
- The fact that there were studies in GERD also should be described, but they needed to be regarded as inconclusive (b) (4). That conclusion should be reported in Section 8.4, Pediatric Use.
- Selected PK/PD data should be included in labeling for patients less than 1 year of age, but this should be included only in Section 8.4 (Pediatric Use), because there was no evidence of efficacy for that age group. Because the EE indication is not being extended below the age of 5 years in the currently recommended labeling, the PK data from the study in patients 5 years and under also should be reported in Section 8.4, rather than in Section 12, Clinical Pharmacology.
- From the recommendations of the Clinical Pharmacology Reviewers, the dosing recommendations should be modified to include weight-based adjustments to dosing, rather than (b) (4).
- Per recommendation of the Clinical Pharmacology Reviewer during the labeling negotiations, the labeling should add a pharmacogenomics section (12.4) recommending a dose reduction in patients if they are known to have the poor metabolizer genotype of CYP2C19 (but without recommending that genotyping be done to determine dosing if the genotype is not already known).

13. Recommendations/Risk Benefit Assessment

Recommended Regulatory Action

The recommended action is approval of the efficacy supplement (S036) for NDA 20-987 (tablets), the associated labeling supplement (S037), and the labeling supplement (S002) for NDA 20-020 (adult granules). The recommended labeling is combined labeling that adds an indication for short-term treatment of erosive esophagitis in patients 5 years and older, reports the negative results for infants from Study 329, and presents selected PK/PD data for patients under 1 year. (See Section 11 for further discussion of the evidence to support these actions, and see Section 12 for further recommendations regarding labeling.)

(b) (4)

Risk Benefit Assessment

Because Study 329 did not provide evidence of efficacy of Protonix for GERD in patients under 1 year, there is no demonstrated benefit to offset the risk of use in that age group, so there should be no recommendation for use in that age group. For older pediatric patients, there is an adequate basis for extrapolating efficacy for healing of EE from adults, and the safety is acceptable.

Recommendation for Postmarketing Risk Management Activities

No special postmarketing risk management activities are recommended for this application.

Recommendation for other Postmarketing Study Commitments or Requirements

During the initial labeling discussions between the FDA and the Applicant, the Applicant expressed willingness to make a commitment to (b) (4)

(b) (4)

(b) (4)

The PMHS recommended, however, that the approval letter remind the Applicant of the notice publication provisions of the BPCA for failure to market pediatric formulations.

Recommended Comments to Applicant

Per PMHS recommendations, the letter for the supplements being approved should include a reminder that the FDA is required under BPCA to publish a notice if an age-appropriate formulation found to be safe and effective under a Written Request is not marketed within one year following the publication of the notice of the exclusivity determination.

The Review Team recommended that PREA Commitment #1 from 11/14/07 for NDA 20-020 could be considered fulfilled, but that Commitment #2 remained unfulfilled. The Division is in the process of assessing the status of pediatric study requirements across the class of PPI products. In view of that ongoing assessment, it is recommended that the approval letter include a statement deferring comment on its determination regarding the status of the PREA commitments.

Recommendation Regarding Future Actions

(b) (4)



Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-20987	SUPPL-36	WYETH PHARMACEUTICA LS INC	PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA-20987	SUPPL-37	WYETH PHARMACEUTICA LS INC	PROTONIX (PANTOPRAZOLE SODIUM) 40MG ENTE
NDA-22020	SUPPL-1	WYETH PHARMACEUTICA LS INC	PROTONIX DELAYED RELEASE GRANULES
NDA-22020	SUPPL-2	WYETH PHARMACEUTICA LS INC	PROTONIX DELAYED RELEASE GRANULES

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

/s/

JOHN E HYDE
11/03/2009