Division Director Summary Review

Date	November 12, 2009
From	Donna Griebel, MD
Subject	Division Director Summary Review
NDA/BLA #, Supplement #	NDA 022020, S001 and S002 NDA 020987, S036 and S037
Applicant Name	Wyeth Pharmaceuticals, Inc./ Pfizer
Date of Submission	Dated November 21, 2008 Received by FDA November 21, 2008
PDUFA Goal Date	May 21, 2009
Proprietary Name / Established (USAN) Name	Protonix / pantoprazole sodium
Dosage Forms / Strength	NDA 022020: Delayed-Release Oral Suspension, 40 mg NDA 020987: Delayed-Release Tablets/ 20 mg and 40 mg
Proposed Indication(s)	(b) (4) .
Action	NDA 02020/S001: (b) (4) NDA 020987/S036 and S037 and NDA 02020/S002:Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Ii-Lun Chen, MD
Statistical Review	Milton Fan, PhD/ Mike Welch, PhD
Pharmacology Toxicology Review	Yuk-Chow Ng, Ph.D./David Joseph, Ph.D.
CMC Review/OBP Review	Sharon Kelly, Ph.D./Hasmukh Patel, Ph.D.
Clinical Pharmacology Review	Insook Kim, Ph.D./Sue-Chih Lee, Ph.D. Li Zhang, Ph.D./Issam Zineh, Ph.D. Justin Earp, PhD./Christoffer W. Tornoe, Ph.D.
DDMAC	Kathleen Klemm PharmD/ Shefali Doshi, MD
CDTL Review	John Hyde, Ph.D., MD
Environmental Assessment	Emily McVey, Ph.D.
SEALD	Paivi Miskala, MSPH, Ph.D. Abiola Olagundoye PharmD/ Laurie Burke, RPh, MPH
DRISK	Latonia Ford, MBA, BSN, RN
DMEPA	Raichell Brown, PharmD, JD/Carol Holquist, R.Ph.
PMHS	Alyson Karesh, MD/ Hari Sachs, MD/Lisa Mathis, MD
DSI	Roy Blay, Ph.D./Constance Lewin, MD, MPH

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
CDTL=Cross-Discipline Team Leader
SEALD = Study Endpoints and Label Development
DRISK = Division of Risk Management

DMEPA = Division of Medication Error Prevention and Analysis
PMHS = Pediatric and Maternal Health Staff
Division of Scientific Investigations

Division Director Review

1. Introduction

This supplemental NDA presented complex regulatory review issues that have been comprehensively summarized and thoroughly discussed in Dr. John Hyde's Cross Disciplinary Team Leader review. The initial submission November 21, 2008, was a supplement to NDA 022020 Protonix For Delayed-Release Oral Suspension. It provided for (b) (4) a PLR conversion. The applicant submitted results from multiple pediatric trials that investigated short-term use of pantoprazole in children ranging in age from preterm infants and neonates through the age of 16 years. The trials were conducted in response to a Pediatric Written Request (WR) and to a post-marketing commitment under PREA to conduct a deferred pediatric study for the treatment of erosive esophagitis associated with gastroesophageal reflux disease in pediatric patients ages birth to 17 years. There is an additional outstanding study commitment under PREA for which the applicant has not conducted a clinical trial: a deferred pediatric study for the maintenance of healing of erosive esophagitis in pediatric patients ages birth to 17 years.

It should be noted that the currently marketed Protonix For Delayed Release Tablet (20mg, 40 mg) and the For Delayed Release Oral Suspension were approved under separate NDAs, but share the same label. NDA 022020 is the NDA for the applicant's currently marketed For Delayed Release Oral Suspension (referred to in this review as the "adult granules"), which is supplied in a 40 mg dosage. The submitted pediatric studies, however, utilized both the new granule formulation ("pediatric granules") and the approved Protonix For Delayed-Release Tablet. In light of this, the FDA asked the applicant during the review cycle to submit an additional efficacy supplement to the NDA for the pantoprazole tablet (NDA 020987).

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(b) (4)

The efficacy supplement for the tablet formulation could be approved, for the indication short term treatment of erosive esophagitis, but only for children 5 years of age and older. The clinical trials in children 5 years and older were conducted with the tablet dosage form.

Labeling supplements to both sNDA 022020 (currently marketed granules) and 020987 (currently marketed tablets), were approved in order to incorporate the safety and pharmacokinetic/pharmacodynamic data from the submitted pediatric studies in the shared label and to incorporate the pediatric indication for acute treatment of erosive esophagitis for children 5 years of age and older. The shared label does not exclude use of the marketed granule formulation (40 mg dose) in children ages 5 and older whose appropriate dose is 40 mg based on their weight.

My review will summarize the major review issues identified by the FDA reviewers and their recommendations for the pantoprazole products' labeling in light of these issues.

2. Background

Protonix has been approved in two different oral formulations:

1) Protonix For Delayed-Release Tablets in two dosage strengths: 20 and 40 mg
2) Protonix For Delayed-Release Oral Suspension, 40 mg. (Each unit dose is a packet that contains 40 mg of enteric-coated granules. This product is referred to in this review as the "adult granules").

The indications for both oral products are:

1) "Short-term Treatment of Erosive Esophagitis associated with Gastroesophageal Reflux Disease (GERD)"….. "indicated for short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis."
2) Maintenance of Healing of Erosive Esophagitis …. "indicated for maintenance of healing of erosive esophagitis and reduction in relapse rates of daytime and nighttime heartburn symptoms in patients with gastroesophageal reflux disease"
3) Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

The dose for each indication is 40 mg each day, with the exception of the Hypersecretory Conditions indication, for which the starting dose is 40 mg twice daily. The 20 mg tablet is marketed for patients who cannot swallow the 40 mg tablet (i.e., those patients take two 20 mg tablets per dose.) There is no current indication for which the dose is 20 mg.

(b) (4)

Pantoprazole does not carry an adult indication for non-erosive GERD.

The studies submitted to support this supplemental NDA included 8 pediatric studies conducted in response to a Pediatric Written Request (WR) issued on December 31, 2001 for Protonix, plus 4 additional supportive studies. The trials, which are summarized in the Tables below [reproduced from Dr. Ii-Lun Chen's Clinical Review (Tables 2-4 of her August 10, 2009 review)], evaluated short-term use of pantoprazole sodium for the treatment of symptomatic GERD in pediatric patients, including preterm infants and neonates through age 16 years. The Agency has concluded that for treatment of erosive esophagitis and non-erosive GERD, efficacy established in adults can be extrapolated to children. Extrapolation is utilized in the 1-17 year olds because the pathophysiology in that population is similar to that in adults. In contrast, for children under the age of 1 year, the FDA has determined that extrapolation from adults is inappropriate since the pathophysiology of GERD in infants is believed to be unique. Symptomatology and prognosis differ between infants and individuals greater than age 1 year. For this reason, the studies requested in the WR in infants less than 12 months of age included a randomized, placebo controlled efficacy study. Although the product does not carry a nonerosive GERD indication, the pediatric studies conducted in response to the Written Request did not restrict enrollment to patients with documented erosive esophagitis.

Table 1: Pediatric Written Request Clinical Outcome and Safety Trials

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-329 PWR Trial 3	US, South Africa, Canada, and several other countries	1 to 11 months	Symptomatic GERD	Granules 1.2 mg/kg placebo	4-week, OL run-in, then 4-week, DB, PC, treatment withdrawal phase	129
3001B3-328 PWR Trial 4	North America	1 to 5 yrs	Endoscopic proven symptomatic GERD	Granules 0.3 mg/kg 0.6 mg/kg 1.2 mg/kg	R, DB, multiple-dose, parallel-treatment for 8 wks	60

Protocol	Location	Age	Population	Formulation	Design	No.
3001A1-322 PWR Trial 4	US	5 to 11 yrs	Endoscopic proven symptomatic GERD	Tablets 10 mg 20 mg 40 mg	R, DB, multiple-dose, parallel-treatment for 8 wks	53
3001A1-326 PWR Trial 5	US	12 to 16 yrs	Symptomatic GERD	Tablets 20 mg 40 mg	R, DB, multiple-dose, parallel-treatment group for 8 wks	136

Table 2: Pediatric Written Request PK and Safety Trials

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-331 PWR Trial 1	Multiple Countries	Neonates and preterm infants	Clinical diagnosis of GERD	Granules 1.2 mg/kg 2.5 mg/kg	R, open-label, single-and multiple-dose PK trial with 2 arms for 5 days	59
3001B3-333 PWR Trial 2	Multiple Countries	1 to 11 months	Presumed GERD	Granules 0.6 mg/kg 1.2 mg/kg	R, open-label, single and multiple-dose, PK, safety and multiple-dose PD trial	67
3001B3-334 PWR Trial 4	US	1 to 11 yrs	Endoscopic proven symptomatic GERD	Granules for ages < 6 yrs Tablets for ages ≥ 6 yrs 0.6 mg/kg 1.2 mg/kg	R, OL, single and multiple-dose, PK trial treated for at least 5 days	41
3001A3-337 PWR Trial 5	US	12 to 16 yrs	Suspected, symptomatic, or endoscopically proven GERD	Tablets 20 mg 40 mg	R, OL, single and multiple-dose, PK trial, treated for at least 5 days	22

Table 3: Supportive Non-Written Request Clinical Trials

Protocol	Location	Age	Population	Formulation	Design	No.
3001B3-335	Multiple Countries	Infants < 12 mos	Presumed GERD	Granules 0.6 mg/kg 1.2 mg/kg	Open-label safety extension trial from 331 or 333	58
3001A1-109	US	5 to 16 yrs	Patients who could benefit from acid suppression	Tablets 20 mg 40 mg	Open-label, single-dose, randomized, parallel group	24

Protocol	Location	Age	Population	Formulation	Design	No.
			therapy			
3001K1-110	US	2 to 16 yrs	Inpatients who could benefit from acid suppression therapy	IV 0.8 mg/kg 1.6 mg/kg	Open-label, single-dose, randomized, parallel group trial	19
3001K1-117	US	1 to 2 yrs	Inpatients who could benefit from acid suppression therapy	IV 0.8 mg/kg 1.6 mg/kg	Open-label, randomized, single –dose trial	4

Although the Exclusivity Board determined on February 13, 2009 that the applicant had met the conditions of the Written Request with the submitted studies, (b) (4)

Pantoprazole granules and tablets do not carry an adult indication for nonerosive GERD. The indication for treatment of GERD in infants was also not supported by the only randomized, placebo-controlled study in that population because the outcome did not demonstrate that pantoprazole was efficacious. Pediatric Exclusivity was granted, effective February 17, 2009.

3. CMC

(b) (4)

4. Nonclinical Pharmacology/Toxicology

I concur with the pharmacology/toxicology reviewers' conclusions that there are no outstanding pharmacology/toxicology issues that preclude approval. I concur with the reviewers' recommendations regarding labeling.

The Pediatric Written Request (WR) included requests for nonclinical studies in juvenile animal models. The submitted studies included:

1) Juvenile rat 25-day oral gavage dose-ranging study
2) Juvenile rat 15-day intravenous dose-ranging study
3) Juvenile rat 15-day intravenous toxicity study
4) Juvenile rat 2-month oral gavage toxicity study
5) Neonatal/juvenile Sprague Dawley rats 4-week oral gavage toxicity study with 3 month recovery period
6) Neonatal Beagle dog 13-week oral gavage tolerability study
7) Neonatal Beagle dog 13-week oral gavage toxicity study with 13-week recovery period
8) Neonatal Beagle dog 1-week oral gavage toxicokinetic study

The stomach was the common target organ of toxicity. The changes in stomach included increased stomach weight in both species, eosinophilic chief cells in the fundic mucosa of rats (a reversible finding), and, in dogs, increased mucosal height with glandular dilation and necrosis, parietal cell hypertrophy, chief cell atrophy and mononuclear cell infiltration. The changes in neonatal dogs (glandular necrosis and inflammatory changes) were noted at all doses studied and were not completely reversible. Dr. Ng noted in his review that pharmacokinetic studies reveal that plasma exposure is higher in younger pups relative to more mature pups (7 day old and 4-week old vs. 13 week old puppies). Oral toxicology studies in adult dogs revealed had that the stomach was one of 3 identified target organs (stomach, liver and lungs). Inflammatory cell infiltration and dilated crypts were observed in adult dogs, but glandular necrosis of the stomach was a unique observation in neonatal pups. He concluded that pantoprazole's effect on neonatal dog stomachs is more severe than in adult dogs.

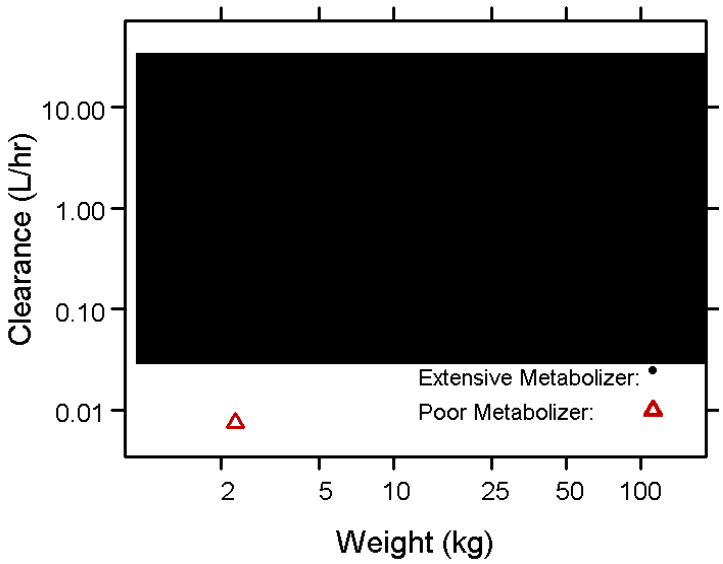
No developmental or growth effects were noted in neonatal/juvenile rats and dogs.

5. Clinical Pharmacology

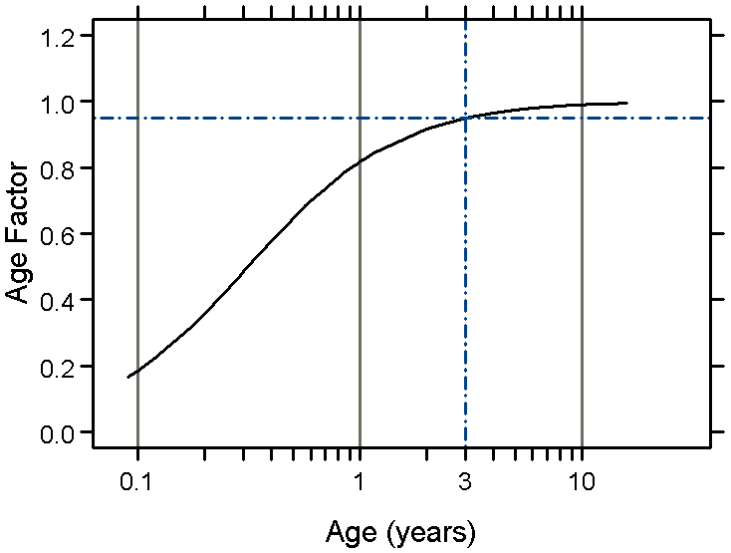
I concur with the conclusions of the clinical pharmacology reviewers. They recommended that the application could be approved "provided mutual agreement on labeling language can be reached between the Agency and the sponsor." They recommended that the product label should incorporate FDA's recommendations for weight-based pediatric dosing and a statement that the dose should be reduced in pediatric patients who are CYP2C19 poor metabolizers.

Analysis of Dosage Recommendations Based on Pharmacokinetic Data

The reviewers noted that inter-individual variation of pantoprazole clearance in children was a function of body weight and age. Population PK analysis suggested that body weight is the key covariate for pantoprazole clearance in children ages 3 years and greater. (See graph below, which is a reproduction of Figure 7 from Dr. Kim's Clinical Pharmacology review and Figure 5 of the Pharmacometric Review in Appendix 4.4 of the Clinical Pharmacology Review.)



Age became a significant factor in infants < 1 year of age. Clearance was reduced 20% in children 1 year of age and was further reduced in younger infants - 80% reduction relative to adults at approximately 1 month of age. In children ages 1 year to 3 years, a diminished effect of age was noted. (See graph below, reproduction of Figure 7 from Dr. Kim's Clinical Pharmacology review.)



Based on their review of the population PK data, the clinical pharmacology reviewers determined that the applicant's proposed (b) (4) would result in AUCs that exceed exposures in adults by nearly 26%, with the highest exposures occurring in children with the lowest body weight in each dose level. The FDA determined that body weight should be utilized to establish pediatric dose recommendations. The following table reproduced from Dr. Kim's Clinical Pharmacology review compares the exposures associated with the dose plan proposed by the applicant versus those associated with the dose plan based on weight and age proposed by the FDA reviewers. The adult exposure is included for comparison. The age and weight dose adjustment recommended by FDA results in exposures comparable to those achieved in adults administered a 40 mg tablet.

Table 4 Pantoprazole Exposure Based on FDA and Applicant Dose Plans Relative to Adult Exposure Associated with a 40 mg Tablet Dose. Results are presented as mean (10th percentile – 90th percentile). Poor metabolizers are excluded from this analysis. (Reproduced from Table 23 in the review by Insook Kim, PhD)

(b) (4)

The applicant agreed to revise the dose recommendations, (b) (4)

(Clinical Reviewer Dr. Ii-Lun Chen noted in the Addendum to her Clinical Review that dosing instructions for patients ages 1 year to 5 years is not possible without an available appropriate dose strength of the granule suspension product. She recommended that (b) (4) a 15 kg minimum weight cut-off be used as the reference for weight-based dosing in developing dosage recommendations for children with the products that are currently marketed, "as this is the lowest 5% weight range for five year-old females". The assumption made in this recommendation is that the smallest 5 year old will be capable of swallowing the 20 mg tablet. In fact, the clinical outcome trials submitted in response to the Pediatric Written Request did utilize age 5 years as the breakpoint between granule and tablet dosage forms. (See Table 1 in this review.) The product label's dosage and administration instructions for children will state:

Children (5 years and older)		
≥ 15 kg to < 40 kg	20 mg tablet	Once daily for up to 8 weeks
≥ 40 kg	40 mg tablet	

The Clinical Reviewer also recommended (b) (4) the label should caution that the 40 mg Protonix For Delayed-Release Oral Suspension packet should not be divided to create a 20 mg dosage form, as the granules are small and the total volume of drug in a 40 mg packet is too small to divide accurately. The Dosage and Administration section of the label will state:

"Do not divide the 40 mg Protonix For Delayed-Release Oral Suspension packet to create a 20 mg dosage for pediatric patients who are unable to take the tablet formulation."

As Dr. John Hyde points out in his CDTL review Section 11 Other Relevant Regulatory Issues, these dosage recommendations do not specifically exclude use of the 40 mg Delayed-Release oral suspension "adult granule" product in children aged 5 years or older who are ≥ 40 kg and who cannot take the tablet. Although the "adult granules" 40 mg dosage form was not studied in the pediatric clinical trials, this formulation has been previously approved at the same dose as the tablet on the basis of comparability established in a pharmacodynamic study.

Issues Related to Pediatric CYP2C19 Poor Metabolizers

The dataset included 6 patients (of 226 patients genotyped) who were CYP2C19 poor metabolizers. Pediatric poor metabolizers had an exposure 6-fold higher than the exposures in pediatric patients who are extensive metabolizers. A similar increase in exposure was seen in a comparison of adult poor metabolizers to adult extensive metabolizers. The prevalence of CYP2C19 poor metabolizers is 3% in Caucasian and African American populations and 17-23% in the Asian population. The clinical pharmacology reviewers recommended that if genotyping is not done, health care providers should consider dose reduction for Asian patients "to the lowest dose level". The ultimate conclusion of the review team was to include the following statement in Section 12.4 Pharmacogenomics of the label:

"For known pediatric poor metabolizers, a dose reduction should be considered."

Pharmacodynamic Data in Infants Less than 12 months of Age

The pharmacodynamic (PD) effects of pantoprazole are of interest in light of the fact that the randomized, controlled trial conducted in infants did not establish that pantoprazole is efficacious for treatment of symptoms of GERD in this young population. Pharmacodynamic evaluation of doses 0.6 mg/kg and 1.2 mg/kg were conducted in infants ages 1-11 months by measuring intragastric and intraesophageal pH at baseline and steady-state. No clear dose-response relationship was observed at these two dose levels. Although 1.2 mg/kg was reported to result in a statistically significant increase in mean and median intragastric pH, the changes at 0.6 mg/kg dose level were not significant, and there was no statistically significant

difference in the changes between the dose groups. Patients in the 0.6 mg/kg group had a higher baseline gastric pH. Their mean gastric pH and percentage time with intragastric pH exceeding pH 4 at baseline were comparable to the values observed after treatment in patients treated with 1.2 mg/kg. The results of this study led to the selection of the 1.2 mg/kg dose level for the efficacy study in infants 1-11 months of age. Among preterm infants and neonates, the PD parameters were only measured at one dose level, and in 5/15 of these preterm infants/neonates the mean intragastric pH exceeded 5 at baseline and the percentage time that their gastric pH exceeded 4 at baseline was 72%-94%.

Issues Related to Bioequivalence of the Available Formulations

Pantoprazole is currently marketed in both a tablet formulation (20 mg and 40 mg) and an oral suspension formulation (in a 40 mg unit dose packet), the "adult granules". The instructions for use of the suspension product include opening the packet and sprinkling on a teaspoonful of applesauce, emptying granules into a cup containing 5 mL of apple juice (the cup should be rinsed 1-2 times with apple juice to remove remaining granules and swallowed), and placing the granules in a nasogastric tube using a syringe and apple juice (at least 30 mL) to rinse the syringe and nasogastric tube.

As discussed in Dr. Kim's Clinical Pharmacology review and summarized in the Dr. Hyde's CDTL review, bioequivalence comparisons of the "pediatric granules" (b) (4) in the initial submission of this sNDA to the approved 40 mg pantoprazole tablet formulation and to the approved 40 mg granules ("adult granules") demonstrated that the "pediatric granules" did not meet strict bioequivalence criteria with either approved formulation. These bioequivalence studies were conducted in adults. In the comparison of the tablet to the "pediatric granules," the two formulations were bioequivalent based on AUC, but the "pediatric granules" fell below the bioequivalence limits for C_{max}. The "pediatric granules" (in applesauce or as a suspension in water) yielded a 34-37% lower C_{max}. See Table 5 below, reproduced from Dr. Kim's Clinical Pharmacology review(Table 4).

Table 5. Mean Pharmacokinetic Parameters for Pantoprazole in Healthy Adults After Single-Dose Administration Of 40 mg Pantoprazole Under Fasted Condition (study 114)

Dosage regimen	Cmax (ng/mL) Mean (% CV) [geometric mean]	Geometric mean ratio to tablet 90% CI	AUC (ng*hr/ml) Mean (% CV) [geometric mean]	Geometric mean ratio 90% CI
Tablet	2958 (31) [2810]	--	6073 (100) [4982]	--
Granules sprinkled on applesauce	1865 (40) [1753]	62.4 (55.62-70.01)	5451 (107) [4498]	90.09 (**84.67-95.85)**
Granules suspended in water	1929 (26) [1855]	66.04 (58.86-74.08)	5629 (106) [4672]	93.8 (88.14-99.78)

* Ratio of Pediatric Granules to Tablet.

In the comparison of the approved 40 mg oral suspension product ("adult granules") vs. the "pediatric granules" (each product sprinkled over applesauce) the reviewers also found that the

two granule products were bioequivalent with respect to AUC but not C_{max}. For C_{max}, the 90% confidence interval for the ratio of the geometric means between the formulations was 108 – 129, which falls outside the targeted 80-125 bioequivalence range. (The "pediatric granules" yielded a lower C_{max}.) The data for this comparison are summarized in the table below, reproduced from Table 5 in Dr. Kim's Clinical Pharmacology review.

Table 6. Mean Pharmacokinetic Parameters For Marketed Granules And Pediatric Granules (N=24)

Dosage regimen	Cmax (ng/mL) Mean (% CV) [geometric mean]	Geometric mean ratio[1] 90% CI	AUC (ng*hr/ml) Mean (% CV) [geometric mean]	Geometric mean[1] 90% CI
Marketed Delayed-Release Oral Suspension	2361 ± 693 [2267]	118 (108-129)	8218 ± 7910 [6112]	106 (100-113)
Pediatric Granules	2036 ± 705 [1916]	--	7963 ± 8032 [5773]	--

[1]Ratio of Delayed-Release Oral Suspension to Pediatric Granules

In comparisons to both approved formulations, the "pediatric granules" were bioequivalent in terms of AUC, but the lower C_{max} associated with the pediatric granules fell outside the range for declaring bioequivalence. I concur with the following conclusion of CDTL Dr. John Hyde regarding the relevance of these differences: "*It should be noted that underdosing with the adult granules by as little as 5% (assuming dose proportionality over this narrow range) would have resulted in ratios falling within the required bioequivalence bounds of 80% to 125% for the comparison of the two granule formulations. Thus, although the adult formulation was not used in the pediatric clinical studies and is not bioequivalent to the one that was, there is an adequate basis in this particular situation for providing dosing recommendations using the adult granule formulation (if made available in pediatric dose strengths) that could produce a pharmaceutical effect equivalent to that of the pediatric granules. Theoretically, a small downward adjustment in the weight-based dosing (which translates into a slight increase in the weight limits used in the dosing table) should be made if the adult granules are to be substituted for the new formulation. As a practical matter, however, given rounding errors, the small size of the adjustment, the substantial variability in exposure at a given dose and over a given age range, and the apparent relatively flat dose-response for effectiveness and safety, the same dosing table could be used for both granule formulations*." (Quoted from the CDTL Review by Dr. John Hyde)

(b) (4)

(b) (4)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical-Efficacy

Four studies were conducted to evaluate the safety and effectiveness of pantoprazole in pediatric patients. Four different age groups were evaluated: Infants to <12 months, 1-5 years, 5-11 years and 12-16 years. The design features are summarized in the table below, a modified reproduction of Table 5 from Dr. Ii-Lun Chen's Clinical Review. The observed outcomes for each age group are discussed in the review subsections that follow.

Table 7: Design Comparison of the Four Clinical Outcome Trials (reproduced and modified from Table 5 of the Clinical Review)

	Infant <1 yr	Age 1-5 years	Age 5-11 years	Age 12-16 years
Double blind, Randomized	X	X	X	X
Placebo	X Randomized withdrawal			
Doses	1.2 mg/kg/day	0.3, 0.6 or 1.2 mg/kg/day	10, 20, or 40 mg per day	20 or 40 mg per day
N (randomized)	108	60	53	136
EE[t] Patients (N)		4	4	
Endoscopy		X	X	
Assessment Tool	CAGS-I	eDiary GSS (GSQ-YC + I-GERQ)	GASP-Q	GASP-Q
Primary Endpoint	Weekly GSS* (five items)	Weekly GSS	CSS (eight items)	CSS

[t] **Documented Erosive Esophagitis**

* Weekly GERD Symptom Score – sum of 5 frequency scores for vomiting/regurgitation, choking/gagging, refusal to eat, difficulty swallowing and abdominal/belly pain.

Infants 1 month to 12 months of age

The only randomized, placebo controlled efficacy study submitted in this sNDA evaluated pantoprazole in infants ages 1 month to <12 months. I concur with the reviewers' conclusions that the outcome observed in this study did not support approval of an indication for treatment of GERD symptoms in infants. The study enrolled infants with symptomatic GERD who entered a run-in phase of non-pharmacologic, conservative treatment. Patients whose symptoms did not improve with conservative treatment were then treated with pantoprazole, open label, for 4 weeks. At the completion of 4 weeks, they were randomized to continue

pantoprazole or to switch to placebo. The efficacy data collected in an eDiary were GERD symptoms, respiratory symptoms, and use of rescue antacid. The assessment instrument, GSQ-I, evaluated five GERD symptoms: 1) vomiting/regurgitation, 2) irritability/fussiness, 3) refusal to feed, 4) choking/gagging, 5) arching back. The eDiary asked for assessment of the five GERD symptoms using a 24-hour recall. The mean weekly GERD symptom frequency was calculated each week.

The primary endpoint was the proportion of patients who withdrew due to lack of efficacy during the randomized treatment-withdrawal phase of the trial. Lack of efficacy was defined as one or more of the following:

> Significant worsening of GERD symptom frequency (i.e., weekly GERD symptom score returned to baseline or above on two consecutive weekly evaluations),
> OR
> Diagnostic test (such as endoscopy) that demonstrates worsening of esophagitis,
> OR
> Maximal antacid used for seven continuous days,
> OR
> Severe GERD symptoms based on physician's judgment,
> OR
> Investigators determine the patient should be withdrawn for lack of efficacy

As shown in the following table reproduced from Dr. Chen's Clinical Review (Table 7 of her review), for the mITT population (N=106) there was no difference between the placebo and the pantoprazole groups in proportion of patients who withdrew.

Table 4: Summary of withdrawal due to lack of efficacy (Trial 329 DB phase)

	Withdrawal/Total	Percent	P-Value
Placebo	6/54	11 %	1.000
Pantoprazole	6/52	12 %	

The Pediatric Gastroesophageal Reflux Clinical Practice Guidelines published in 2001 by the North American Society for Pediatric Gastroenterology and Nutrition in the Journal of Pediatric Gastroenterology and Nutrition, Volume 32, Supplement 2 have been endorsed by the American Academy of Pediatrics. They state that the primary goals of therapy for GERD "are to relieve the patient's symptoms, promote normal weight gain and growth, heal inflammation caused by refluxed gastric contents (esophagitis), and prevent respiratory and other complications associated with chronic reflux of gastric contents". They point out that gastroesophageal reflux (GER) is a normal physiological process that occurs in healthy people, including infants, and that in GERD the reflux causes symptoms. The manifestation of GER in infants is vomiting/spitting up. The symptoms of infants with GERD reported in this publication are painful swallowing, difficulty swallowing, arching of back during feedings, irritability, anorexia, failure to thrive, hematemesis, and anemia.

Infants in the submitted efficacy study were enrolled in the study if they had been diagnosed with GERD. The underlying physiology of the clinical entity called GERD in infants is not

clearly the same as it is in adults, and exposure of the esophagus to gastric pH may not entirely explain the symptoms in this young population, at least not in all infants. Raising gastric pH with PPIs, may only address a fraction of the underlying etiology of these infants' symptoms. The Agency has not extrapolated efficacy in adults to infants less than 12 months of age.

Pediatric Patients ages 1 year to 16 years

For children ages 1-16 years, the Agency has extrapolated efficacy of short-term treatment of erosive esophagitis associated with GERD from adult efficacy data. The study designs for the 3 trials conducted in children ages 1 year – 16 years were parallel group, double-blind, randomized trials that evaluated varying pantoprazole doses administered for 8 weeks. The primary endpoint was improvement of symptoms associated with GERD, not healing of erosive esophagitis. Although inclusion criteria for the two trials that enrolled patients ages 1 year through 5 years and ages 5 years through 11 years required endoscopically proven symptomatic GERD, the study for patients 12 years through 16 years did not. Only 8 patients across the studies had endoscopically documented erosive esophagitis, but all 8 had documented healing of their erosive esophagitis in the trials.

I concur with the review team that efficacy for erosive esophagitis can be extrapolated for the erosive esophagitis indication from adults to children one year and older. (b) (4) d.

The current Protonix product indication for treatment of erosive esophagitis associated with GERD reads as follows:

> "Short-term Treatment of Erosive Esophagitis associated with Gastroesophageal Reflux Disease (GERD)"….. "indicated for short-term treatment (up to 8 weeks) in the healing and symptomatic relief of erosive esophagitis."

It also carries an indication for maintenance of healing of erosive esophagitis. Protonix does not carry a broad indication for treatment of GERD, which incorporates nonerosive GERD. This fact was considered by the reviewers in developing appropriate pediatric labeling. Although the efficacy assessments in the pediatric studies conducted in response to the WR were generally limited to GERD symptom assessments, not endoscopic evaluation of erosive esophagitis, and only a small subset of the patients in the pediatric studies had documented erosive esophagitis, the current pantoprazole indication labeling sets the limits for extrapolation of efficacy from adults to the pediatric population. (b) (4)

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(b) (4)

. Labeling and associated efficacy evaluations for GERD and erosive esophagitis for available PPI products are summarized in the table in this review's Appendix.

8. Safety

I concur with Dr. Chen's conclusion that there were no safety signals of concern in the data submitted.

The pediatric safety database included a total of 614 pediatric patients who received at least one dose of pantoprazole: 333 received granules, 258 received tablets, and 23 received the IV formulation. Those in the tablet group received a mean of 41 doses. The mean age of children in the trials was 5.8 years (range birth to 16 years). The safety population was 57% male and 47% female; 75% Caucasian, 18% African American, and approximately 8% Hispanic.

There was one death reported in a child who participated in a supportive trial (intravenous pantoprazole). This patient, a seven-year-old, was hospitalized for a closed head injury secondary to a fall sustained prior to study enrollment. He received two doses of IV pantoprazole 1.6 mg/kg while on study, and five days after completing the study, he experienced progressive neurologic deterioration as a complication of the closed head injury. He had respiratory failure requiring mechanical ventilation and died. The reviewer agreed that this AE was unrelated to pantoprazole.

There were 23 (4%) patients who experienced at least one SAE. None of the SAEs was considered to be related to pantoprazole by the investigators. The event most commonly reported as an SAE was viral gastroenteritis, which was reported in 3 (0.5%) infant patients. In two patients, seven events were each reported as SAEs (worsening of GERD, vomiting, dehydration, bronchiolitis, respiratory failure, stridor and otitis media). In the 4 clinical outcome studies submitted, the SAEs were primarily reported in the infant trial. The SAEs in the infant trial included: respiratory (4), digestive (3), metabolic and nutritional (2), cardiovascular (1), and special senses (1).

Overall, 412 (67%) patients reported one or more treatment emergent adverse events (TEAEs). The most commonly reported TEAEs were headache (12%), URI (12%), rhinitis (10%), infection (9%), fever (8%), diarrhea (8%), accidental injury (7%), pharyngitis (7%) abdominal pain (6%), cough (6%), vomiting (6%), and otitis media (5%). In the infant trial, the only

placebo controlled trial, the adverse reactions reported more commonly (difference of ≥ 4%) in the treated population compared to placebo included: otitis media, rhinitis, and laryngitis.

Dr. Chen evaluated the safety dataset for evidence of a relationship between dose administered and events. She noted that "Overall, 452 (73.6%) patients reported one or more AEs, including 35 (94.6%) patients in the low dose group, 146 (69.2%) in the medium dose group, and 271 (74.0%) in the high dose group. One or more TEAEs were reported in 412 of 614 (67.1%) patients: 94.6% of patients who received low dose pantoprazole, 64.0% of patients who received medium dose, and 66.1% of patients who received high dose." She noted that "the higher rate of TEAEs in the low dose group may reflect the longer mean duration of therapy received by those patients (approximately 56 days) as compared to the shorter duration of therapy for patients in the medium and high dose groups (approximately 37 days each)."

Dr. Chen observed that there were two events for which the frequency of TEAEs appeared to increase with increased dose - otitis media (reported in 2.7%, 2.8%, and 6.6% of patients in the low, medium, and high dose groups, respectively) and contact dermatitis (reported in 0, 2.4%, and 3.8% of patients in the low, medium, and high dose groups, respectively). However, she noted that the majority of otitis media and contact dermatitis events occurred among infants, 83% of whom received high dose pantoprazole. I concur with her conclusion that "The apparent dose response observed for the overall analysis may represent an artifact of data pooling resulting from the relatively high incidence of otitis media and contact dermatitis in the infant population, and the disproportionate number of patients in this age group who received treatment with high dose pantoprazole". Dr. Chen noted that, in contrast to otitis media and contact dermatitis, the frequencies of other TEAEs decreased with increasing dose. Among these were headache (27%, 15.2%, 9.0%), infection (13.5%, 11.4%, 6.3%), accidental injury (18.9%, 9.5%, 4.4%), and pharyngitis (13.5%, 7.6%, 5.7%), all of which were reported more commonly in the older age groups, which included all of the patients receiving low dose and a larger proportion of those who received the "mid-range" dose of pantoprazole.

I concur that there is sufficient evidence of safety to support approval of pantoprazole for short term treatment of children ages 1 year and older.

9. Advisory Committee Meeting

There was no advisory committee meeting for this application. Pantoprazole is not a new molecular entity and there were no issues identified that required discussion with external experts.

10. Pediatrics

See Dr. Chen's Clinical Review for a detailed history of the Written Request and the applicant's response to the Written Request. The Pediatric Exclusivity Board met on 2/13/2009. They concluded that the studies met the requirements of the Pediatric WR. Pediatric Exclusivity was granted, effective 2/17/2009.

The application was presented to the Pediatric Research Committee (PeRC) on 4/22/2009. The PeRC recommended that the lack of efficacy demonstrated in infants less than 1 year of

age should be clearly stated in the product label. The committee recommended that the results of the placebo controlled trial conducted in infants and the pharmacokinetic data for this population should be included in the Pediatric Use section of the product label. (See Section 12 Labeling of this review, below.)

The original NDA 022020's 11/14/07 Approval Letter included the following pediatric study requirements under PREA (NDA 020987 has no outstanding PREA commitment):

1. Deferred pediatric study for the treatment of erosive esophagitis associated with gastroesophageal reflux disease in pediatric patients ages birth to 17 years. (Final Report Submission : December 31, 2008)
2. Deferred pediatric study for the maintenance of healing of erosive esophagitis in pediatric patients ages birth to 17 years. (Final Report Submission December 31, 2008).

I concur with the reviewers that the PREA requirement study #1 has been completed. Although the placebo controlled infant study submitted did not include infants younger than 1 month, I agree with the reviewers that it is impracticable to study this very young age group given the time needed to establish the diagnosis and to determine whether pharmacologic intervention is needed. The clinical reviewers, however, did not conclude that the PREA requirement study #2 has been adequately addressed in this application. The clinical reviewer did not find that the literature review submitted by the applicant was adequate to support the safety of use of pantoprazole in children for maintenance of healing of erosive esophagitis, for which dosing would be more chronic in nature. The CDTL concurred that PREA commitment #2 should not be considered fulfilled. The extent of safety data required to support use of pantoprazole for maintenance of healing of erosive esophagitis in children will be discussed further with the Pediatric and Maternal Health Staff medical officers before making a final decision regarding the status of PREA commitment #2. This issue may require presentation to the PeRC. The approval letter will state that the FDA will contact the applicant regarding the final status of these PREA commitments in a separate letter.

11. Other Relevant Regulatory Issues

DSI inspected the two sites with the largest number of participants in this submission across age groups. The DSI inspector determined that the data at each site were acceptable in support of the applications.

The clinical reviewer found that the applicant submitted a form 3454 certifying there was no financial arrangement with the clinical investigators whereby the value of the compensation to the investigator could be affected by the outcome of the trial, as defined in 21 CFR 54.2(a).

(b) (4)

(b) (4)

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12. Labeling

The DDMAC reviewers, Study Endpoints and Label Development (SEALD) team, and Division of Risk Management (DRISK) evaluated the proposed product label. Their review recommendations contributed to labeling negotiations with the applicant. The Division of Medication Error Prevention and Analysis (DMEPA) reviewers evaluated the carton and container labels. (b) (4)

Given that efficacy was not established in the clinical trial conducted in infants less than 12 months of age, Section 8.4 Pediatric Use of the Protonix Delayed-Release Oral Suspension and Delayed-Release Tablets shared label was revised to state that "Effectiveness for EE has not been demonstrated in patients less than 1 year of age." A subsection of Section 8.4, *Neonates to less than one year of age*, opens with the statement "Protonix was not found to be effective in a multicenter, randomized, double-blind, placebo-controlled, treatment-withdrawal study of 129 pediatric patients 1 through 11 months of age." This subsection also provides the pharmacokinetic and pharmacodynamic data obtained in the infant subpopulation. Information on the higher AUC observed in preterm infants and neonates was considered important for safety and provided context for pharmacodynamic data. Section 8.4 ends with the statement "Because Protonix was not shown to be effective in the randomized, placebo-controlled study in this age group, the use of Protonix for treatment of symptomatic GERD in infants less than 1 year of age is not indicated."

The trials that support the pediatric indication for erosive esophagitis in children ages 5 years and older are presented in Section 14 Clinical Studies of the labels under subsection 14.1 Erosive Esophagitis (EE) Associated with Gastroesophageal Reflux Disease (GERD). The label clearly states that the efficacy in pediatric patients ages 5 years through 16 years is extrapolated from adequate and well-conducted trials in adults "as the pathophysiology is thought to be the same". It notes that 4 children with endoscopically diagnosed erosive esophagitis were treated in this age group and healing was documented in all 4 at 8 weeks. The pharmacokinetic data from this pediatric subpopulation, for whom the product will carry a pediatric indication, were placed in Section 12.3 Pharmacokinetics of the label.

Because there will be no age appropriate formulation marketed for children ages 1 year to 5 years, the clinical trial data and pharmacokinetic data for this population, for whom Protonix will not carry an indication, were placed in Section 8.4 Pediatric Use. This section will include the statement, "Although the data from the clinical trials support use of Protonix for the short-term treatment of EE associated with GERD in pediatric patients 1 year through 5 years, there is no commercially available dosage formulation appropriate for patients less than 5 years of age. [*see Dosage and Administration (2).*]"

It is impossible to accurately divide the 40 mg granule packaged dose and it is possible that young children could be treated inadvertently with a dose that exceeds the recommended dose in this age group if this were to be attempted. The Dosage and Administration section states "Do not divide the 40 mg Protonix For Delayed-Release Oral Suspension packet to create a 20 mg dosage for pediatric patients who are unable to take the tablet formulation.

For children ages 1 though 16, in order to clarify the discrepancy between the condition studied in clinical trials compared to the more limited condition described in the product's labeled indication – symptomatic GERD vs. Erosive Esophagitis - Section 8.4 Pediatric Use of the label will state, "Because EE is uncommon in the pediatric population, predominantly pediatric patients with endoscopically-proven or symptomatic GERD were also included in these studies…… Because these pediatric trials had no placebo, active comparator, or evidence of a dose response, the trials were inconclusive regarding the clinical benefit of PROTONIX for symptomatic GERD in the pediatric population. The effectiveness of PROTONIX for treating symptomatic GERD in pediatric patients has not been established."

I concur with the Clinical Pharmacology reviewers' recommendations that the dosing recommendations should include weight-based dosing. I also concur that labeling should include a Pharmacogenomics Section 12.4 that recommends considering dose reduction in pediatric patients that are known to be CYP2C19 poor metabolizers.

13. Decision/Action/Risk Benefit Assessment

- Regul
  - (b) (4)

(b) (4)

- I concur with the reviewers that the applicant should be issued an approval for the efficacy supplement for NDA 020987 (Protonix Delayed-Release Tablet) for the indication for short-term treatment of erosive esophagitis associated with GERD in patients 5 years and older, based on the clinical trials that were conducted in this population and extrapolation of efficacy established in adults from adequate and well-controlled trials. In addition, approvals should be issued for the labeling supplement for NDA 020987 and the labeling supplement for NDA 022020, which provide for updating the combined labeling for the tablet and oral suspension Protonix products to incorporate pediatric information.

- I concur with the reviewers that the randomized, placebo controlled study that evaluated the efficacy of pantoprazole for treatment of GERD in infants less than 12 months of age did not provide evidence of efficacy in this population. Extrapolation of efficacy from adults in this population is not appropriate.

- Risk Benefit Assessment

The efficacy study conducted to demonstrate that Protonix is effective for treatment of GERD in infants less than 1 year of age did not establish efficacy of the product in this population. Efficacy cannot be extrapolated from adults in this age group. Approval for this indication in this population cannot be justified given the lack of evidence of efficacy to offset any risk that could be associated with use of this product in this very young age group.

For ages 1 year and older, the efficacy of pantoprazole, which has been previously established in adults for the indication treatment of erosive esophagitis, can be extrapolated (i.e., to age 1 year and older). The studies submitted support the safety of use of pantoprazole for short term treatment of erosive esophagitis. (b) (4) the product label will clearly state that the available 40 mg suspension dose should not be divided.

- Recommendation for Postmarketing Risk Management Activities
  None recommended.

- Recommendation for other Postmarketing Study Commitments
  The approval letters will remind the Applicant of the notice publication provisions of the BPCA for failure to market pediatric formulations. (b) (4)

(b) (4)

Appendix:

Drug	Indications	Supporting Studies	Pediatric Indication	Supporting Studies
Esomeprazole	1.1 Treatment of GERD for which there are 3 subheadings: 1)indicated for short term treatment (4-8 weeks) in healing and symptomatic resolution of diagnostically confirmed erosive esophagitis 2) indicated to maintain symptom resolution and healing of erosive esophagitis. 3) indicated for short-term treatment (4-8 weeks) of heartburn and other symptoms associated with GERD *in adults* and children 1 year and older.	4 clinical trials evaluated healing of erosive esophagitis Two RCTs evaluated GERD symptoms in patients without erosive esophagitis. .	3) indicated for short-term treatment (4-8 weeks) of heartburn and other symptoms associated with GERD in adults *and children 1 year and older.*	Extrapolation from adult studies and the safety and pharmac studies performed in pediatric and adolescent patients
Lansoprazole	1.7 GERD, for which there are two subheadings 1)indicated for the treatment of heartburn and other symptoms associated with GERD 2) indicated for short-term treatment (up to 8 weeks) for healing and symptom relief of all grades of erosive esophagitis. 1.8 Maintenance of Healing of Erosive Esophagitis	A study of patients with GERD, but no esophageal erosions by endoscopy. Trials evaluated healing and symptoms in patients with endoscopic erosive esophagitis. Two adult trials evaluated maintenance of healing endoscopically.	Short-term treatment of symptomatic GERD in children 1-17 year old Short-term treatment of erosive esophagitis in children 1-17 years of age.	Open label study in children ages 1-11 years (N=66) include with GERD symptoms (85%), endoscopically documented e esophagitis (42%) and 58% with nonerosive GERD. In the 12-17 year old age group an uncontrolled study (N=87 patients with nonerosive GERD (74%) and erosive esophagi Erosive esophagitis healing was endoscopically documented healing rate in the 1-11 year old study was 100% and 96% in adolescent study.
Omeprazole	1.3 Treatment of GERD in "*adults* and pediatric patients" with subsection indications 1) "indicated for the treatment of heartburn and other symptoms associated with GERD in pediatric patients and *adults*"	Trial in adult patients with "symptomatic GERD" without erosive esophagitis	1.3 Treatment of GERD in "adults and *pediatric patients*" with subsection indications 1) "indicated for the treatment of heartburn and other symptoms associated with GERD in *pediatric patients* and adults"	Symptomatic GERD studied in patients ages 1-16 years with suggestive of nonerosive GERD" in a single arm trial in whi were assessed.

Drug	Indications	Supporting Studies	Pediatric Indication	Supporting Studies
	2) "indicated for the short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy in pediatric patients and *adults*". 1.4 Maintenance of Healing of Erosive Esophagitis (*adults* and "pediatric patients").	Erosive esophagitis study in adults with Healing and symptom outcomes Two long term maintenance of healing of erosive esophagitis studies in adults.	2) "indicated for short-term treatment (4-8 weeks) of erosive esophagitis diagnosed by endoscopy in *pediatric patients* and adults". 1.4 Maintenance of Healing of Erosive Esophagitis (adults and "*pediatric* patients").	Healing of erosive esophagitis studied in a single arm study ages 1-16 years (N=57) with documented erosive esophagiti was documented in 90%. Symptoms were also assessed. **An open label study of maintenance of healing of erosive was conducted in 46 children.** Different doses were utilize study and 41% of patients had no relapse. Of the 46 patien 46% who started at half the dose found to be effective for he required an increase of dose during maintenance. (Study 214 was a 28 day study that evaluated multiple condi including nonerosive GERD and 3 patients with erosive esop enrolling patients ages 2 years to16 years. Study 678 enrolle with erosive esophagitis ages 1 year to 16 years, and had a m of healing evaluation phase.)
Rabeprazole	1.1 Healing of Erosive or Ulcerative GERD (4-8 weeks of treatment in the healing and symptomatic relief of erosive or ulcerative GERD.) 1.2 Maintenance of Healing of Erosive of Ulcerative GERD (controlled studies don't extend beyond 12 months.) 1.3 Treatment of Symptomatic GERD (daytime and nighttime heartburn and other symptoms associated with GERD) in *adults* and adolescents 12 years of age and above.	Maintenance of healing was assessed at 52 weeks. Endpoints = healing and symptoms assessment. Treatment of symptomatic GERD studies conducted in patients without evidence of erosive esophagitis on baseline endoscopy.	1.3 Treatment of Symptomatic GERD (daytime and nighttime heartburn and other symptoms associated with GERD) in adults and *adolescents 12 years of age and above*.	Treatment of GERD in adolescents supported by a) extrapola results from adult studies and; b) safety and pharmacokinetic adolescent patients. A randomized, open-label, parallel-gro enrolled 111 adolescents with a clinical diagnosis of sympto or suspected or endoscopically proven GERD. Two dose lev studied. Treatment lasted up to 8 weeks. The Pediatric Us the product label, which discusses the use of extrapolation, d the adult indication sections for erosive esophagitis, mainten healing of erosive esophagitis and the GERD indication, hov the GERD indication mentions that the product is indicated f adolescents with that specific condition.
Dexlansoprazole	1.1 Healing of erosive esophagitis for	Healing assessed	No Pediatric labeling	PMRs for the following:

Drug	Indications	Supporting Studies	Pediatric Indication	Supporting Studies
	up to 8 weeks 1.2 Maintenance of Healed Erosive Esophagitis for up to 6 months. 1.3 Treatment of Symptomatic Non-Erosive Gastroesophageal Reflux Disease, heartburn associated with non-erosive gastroesophageal reflux disease (GERD) for 4 weeks.	endoscopically at 4 and 8 weeks. Maintenance of healing assessed endoscopically at 6 months. Symptoms also assessed. Symptoms assessed at 4 weeks for the non-erosive GERD indication.		Deferred studies of **healing and maintenance** of erosive es ages 1year to 11 year and 12 to 17 years. Deferred studies for treating heartburn associated with non-e esophagitis for ages 1 month – 11 months, 1 year to 11 years to 17 years.

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

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/s/

DONNA J GRIEBEL
11/12/2009