DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-987
NDA 20-988

Wyeth-Ayerst Laboratories
Attention: Caroline Henesey, PhD
P.O. Box 8299
Philadelphia, PA 19101-8299

Dear Dr. Henesey:

Reference is made to your Proposed Pediatric Study Request submitted on January 19, 2001 for New Drug Application (NDA) 20-987, Protonix® (pantoprazole sodium) Delayed-Release Tablets, and NDA 20-988, Protonix® I.V. (pantoprazole sodium) for Injection.

To obtain needed pediatric information on pantoprazole sodium, the Food and Drug Administration (FDA) is hereby making a formal Written Request, pursuant to Section 505A of the Federal Food, Drug, and Cosmetic Act (the Act), that you submit information from the studies described below.

As used in this written request, a *preterm infant* is an infant who has completed less than 38 complete weeks of gestation. A *term infant* is an infant that has completed 38-42 weeks gestation, and a *post-term infant* is an infant that has completed more than 42 weeks gestation. For preterm infants, *corrected age* is the sum of the gestational age and the age since birth. For example, a preterm infant born after 32 weeks gestation for which 12 weeks have elapsed since birth has a corrected age of 44 weeks. The *neonatal period* is the first 28 days since birth.

TYPE OF STUDIES:

The Division of Gastrointestinal and Coagulation Drugs has concluded that the course of gastroesophageal reflux disease (GERD) in adults is not sufficiently similar to the course of pathological gastroesophageal reflux in pediatric patients less than one year of age to permit extrapolation of the adult efficacy data to this pediatric age group. The effects of pantoprazole sodium, both beneficial and adverse, may also differ in adults from those in patients less than one year of age. Therefore, to fulfill the conditions of this written request, efficacy studies must be performed in pediatric patients less than one year of age (see Studies 2 and 4).

STUDY 1: PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD), AND SAFETY STUDY IN NEONATES AND IN PRETERM INFANTS WITH A CORRECTED AGE LESS THAN 44 WEEKS

Inclusion criteria: To be included in this study, infants will (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery, (b) have evidence of obstructive apnea by pneumographic monitoring, (c) be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (d) either be term or post-term infants within the neonatal period, or

be preterm infants with a corrected age of less than 44 weeks, and (e) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in the study.

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of pantoprazole sodium. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 24 patients (i.e., at least 12 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose PK, PD, and safety study of pantoprazole sodium. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete this part of the study if a standard PK approach is used. Alternatively, a population PK approach may be used given difficulties in obtaining adequate samples in small infants with a limited circulating blood volume. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six of these (or other) patients who require tube placement or pH monitoring for clinical management not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

STUDY 2: EFFICACY AND SAFETY STUDY IN NEONATES AND IN PRETERM INFANTS WITH A CORRECTED AGE OF LESS THAN 44 WEEKS

Inclusion criteria: To be included in this study, patients must meet the same inclusion criteria specified above for Study 1.

- **Design:** This will be a multicenter, treatment-withdrawal study of the efficacy and safety of pantoprazole sodium in which treatment withdrawal is randomized, double-blind, and placebo-controlled. The dosage(s) of pantoprazole sodium used in this study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 1 and as suggested by the results of other studies (e.g., literature studies of pediatric patients). Patients will be stratified by whether or not they are receiving methylxanthine (e.g., theophylline, caffeine) for treatment of central apnea and by corrected age. Protocol design will also consider whether or not patients receive concomitant prokinetic agents (e.g., metoclopramide, erythromycin). The number of patients per treatment group required to complete the study is described in the Statistical Information section. Independent data review committees (e.g., for safety, efficacy, or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

- **Run-in phase:** All patients will receive pantoprazole sodium in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by pantoprazole sodium is at

steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this part of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

- **Withdrawal phase**: At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of pantoprazole sodium or to receive matching placebo. Following randomization, patients will be monitored closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

Therapy for central apnea will be tracked. Individuals such as caregivers, who will be making observational assessments of apnea or bradycardia, will be trained appropriately in apnea/bradycardia monitoring procedures. Additionally, cardiorespiratory monitors used to assess apnea and bradycardia will be capable of recording and storing each patient's data for the duration of the study.

STUDY 3: PHARMACOKINETIC, PHARMACODYNAMIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

Inclusion criteria: To be included in this study, infants will (a) be hospitalized patients considered to be candidates for acid suppressive therapy because of a presumptive diagnosis of GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in the study.

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of pantoprazole sodium. Adequate justification for dose selection will be provided. Patients will be allocated to treatment groups in approximately equal proportions. At least 20 patients (i.e., at least 10 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated dose PK, PD, and safety study of pantoprazole sodium in pediatric patients. The study will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of pantoprazole sodium. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. At least 12 patients per treatment group will complete pharmacokinetic assessments if a standard PK approach is used. Alternatively, a population PK approach may be used. Pharmacodynamic assessments of intragastric and/or intraesophageal pH will be performed in at least six of these (or other) patients who require tube placement or pH monitoring for clinical management not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

STUDY 4: EFFICACY AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 MONTHS OF AGE

Inclusion criteria: To be included in this study, infants will (a) be patients with a clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD, and (b) either be a term or post-term infant beyond the neonatal period but less than 12 months of age, or else be a preterm infant with a corrected age of at least 44 weeks but less than 12 months. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

The method by which the clinical diagnosis of suspected GERD, symptomatic GERD, or endoscopically proven GERD is made will be recorded and summarized for each patient. These summaries will include the clinical history and results of laboratory tests used to establish the diagnosis (e.g., pH probe, gastroesophageal endoscopy, radionuclide milk study). Results from such laboratory tests will be provided regardless of whether they supported the final clinical diagnosis or not.

- **Design:** This will be a multicenter, treatment-withdrawal study of the efficacy and safety of pantoprazole sodium in which treatment withdrawal is randomized, double-blind, and placebo controlled. The dosage(s) of pantoprazole sodium used in this study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Study 3, and as suggested by the results of other studies (e.g., literature studies of pediatric patients). The number of patients per treatment group required to complete the study is described in the Statistical Information section. Independent data review committees (e.g., for safety, efficacy, or both) may be established to review accumulating data to detect early evidence of great benefit or harm of treatment.

- **Run-in phase:** All patients will receive pantoprazole sodium in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by pantoprazole sodium is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this part of the study (e.g., lack of therapeutic response, adverse event) will be captured in detail.

- **Withdrawal phase:** At the conclusion of the run-in phase, patients will be randomly assigned (in approximately equal proportions) in a double-blind fashion to continue receiving their current dosage of pantoprazole sodium or to receive matching placebo. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes.

Following randomization, patients will be followed closely to allow for prompt discontinuation from randomized study treatment if clinically appropriate. The protocol will define discontinuation criteria

for patients who have adverse events or fail therapy during the withdrawal phase. Patients who are removed from randomized study treatment will be given appropriate alternative medical therapies.

STUDY 5: PHARMACOKINETIC, EXPOSURE/RESPONSE, AND SAFETY STUDY IN PEDIATRIC PATIENTS 1 TO 11 YEARS OF AGE

Inclusion criteria: To be included in this study, patients will (a) be 1 to 11 years of age inclusive, (b) have endoscopically proven GERD, and (c) have had endoscopic examination as part of their diagnostic evaluation. Patients of both sexes will be enrolled in the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from the study.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of pantoprazole sodium. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of pantoprazole sodium. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Exposure/Response Component:

This will be a randomized, double blind, dose-ranging study of pantoprazole sodium. The dosages of pantoprazole sodium used in this study will be selected as dosages likely to be therapeutically effective and safe, based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Eligible patients will be randomized in approximately equal proportions to one of at least three dose levels of pantoprazole sodium. After randomization, the overall duration of the trial will be at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 40 patients 1 to 5 years of age and 40 patients 6 to 11 years of age will complete at least 8 weeks treatment.

STUDY 6: PHARMACOKINETIC AND SAFETY STUDY IN PEDIATRIC PATIENTS 12 TO 16 YEARS OF AGE

Inclusion criteria: To be included in this study, patients will (a) be 12 to 16 years of age inclusive, and (b) have a clinical diagnosis of suspected GERD, symptomatic GERD or endoscopically proven GERD. Endoscopy is not required for study entry or participation. Patients of both sexes will be enrolled in the single- and repeated-dose components of the study as well as in the eight-week safety component.

Pharmacokinetic Component:

Part 1 (single dose): This will be a randomized, single-dose pharmacokinetic and safety study of at least two dose-levels of pantoprazole sodium. Patients will be allocated to treatment groups in approximately equal proportions. Adequate justification for dose selection will be provided. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Part 2 (repeated dose): This will be a repeated-dose pharmacokinetic and safety study of at least two dose-levels of pantoprazole sodium. Patients will be randomly allocated to treatment groups in approximately equal proportions. The dose level(s) and frequency of dosing used in this part of the study will be selected based on results from Part 1. At least 12 patients (i.e., at least 6 per treatment group) will complete this part of the study if standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

Eight-week Safety Component:

This will be a multicenter safety study of pantoprazole sodium. An open-label, non-randomized design is acceptable. Dosages of pantoprazole sodium used in this study will be selected as dosages likely to be therapeutically effective and safe based on data from the pharmacokinetic component of this study as well as from other studies in pediatric patients and adults. Patients will be treated for at least eight weeks. Outcome measures will be assessed weekly: at clinic visits that occur at least once every other week, as well as by other appropriate means (e.g., telephone questionnaire) during weeks in which no clinic visits are scheduled. For example, telephone evaluations may be made to assess compliance, adverse events, and other clinical outcomes. At least 100 patients will complete at least eight weeks of treatment.

INDICATION TO BE STUDIED:

Treatment of gastroesophageal reflux disease (GERD)

OBJECTIVES AND RATIONALE:

Studies 1 and 3:

(a) To characterize the pharmacokinetic/pharmacodynamic profile of single and repeated doses of pantoprazole sodium and to compare these profiles with those in adults and older pediatric patients.

(b) To collect information on the safety of single and repeated doses of pantoprazole sodium.

Study 2:

(a) To obtain efficacy data as measured by obstructive apnea for pantoprazole sodium in preterm infants and neonates.

(b) To assess the safety of pantoprazole sodium in preterm infants and neonates.

Study 4:

(a) To obtain efficacy data for pantoprazole sodium in pediatric patients 1 to 11 months of age.

(b) To assess the safety of pantoprazole sodium in pediatric patients 1 to 11 months of age.

Study 5:

(a) To characterize the pharmacokinetic profile of single and repeated doses of pantoprazole sodium in patients 1 to 11 years of age.

(b) To compare the safety and clinical outcome of pediatric patients 1 to 11 years of age with endoscopically proven GERD across different dosages of pantoprazole sodium.

(c) To determine the proportion of patients showing endoscopic evidence of healing after completion of therapy across different dosages of pantoprazole sodium in those pediatric patients 1 to 11 years of age who undergo follow-up endoscopy after treatment.

Study 6:

(a) To characterize the pharmacokinetic profile of single and repeated doses of pantoprazole sodium in patients 12 to 16 years of age.

(b) To collect information on the safety of single and repeated doses of pantoprazole sodium in pediatric patients 12 to 16 years of age.

STUDY EVALUATIONS AND ENDPOINTS:

Pharmacokinetics: In the PK studies, appropriate pharmacokinetic parameters will be assessed for both the single- and repeated-dose portions of the studies (e.g., AUC, apparent clearance, T_{max}, $T_{1/2}$, apparent volume of distribution, C_{max}, and others as appropriate).

Pharmacodynamics: In the PD studies, appropriate pharmacodynamic parameters will be assessed (e.g., AUC of the gastric H+ concentration over time, intraesophageal pH, gastric pH, percentage of time gastric pH>4, and percentage of time gastric pH>3). Pharmacodynamic assessments will be made just prior to dosing and at appropriate intervals after dosing to encompass the duration of drug effect. For patients receiving repeated doses, pharmacodynamic assessments will be made at baseline (i.e., before therapy) and after the final pantoprazole sodium dose.

Safety and tolerability: In each study, the evaluation of safety will include a physical examination and clinical laboratory assessment before treatment and, at a minimum, after completion of the pharmacokinetic, pharmacodynamic, or clinical-outcome assessments. Assessment of adverse events will occur throughout each patient's study participation. Patients will be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure will be documented fully, as will the use of any rescue medications. All patients will be followed at least 2 weeks after final administration of test medication. Patients enrolled in the studies 2 and 4 will undergo follow-up developmental, growth, and safety assessments 6 and 12 months after enrollment.

Other clinical outcomes and endpoints:

Study 1: Apnea and bradycardia will be assessed concurrent to pHmetry.

Study 2: Respiratory signs and symptoms, including apnea and bradycardia, will be monitored. The primary outcome measure will be obstructive apnea assessed by repeat pneumogram (s) following patient enrollment.

Additional outcome parameters: patient discontinuations due to ineffective treatment, apnea as assessed by conventional cardio-respiratory monitoring and nursing observations, severity of apneic episodes (e.g., as manifested by drop in O_2 saturation, cyanosis, bradycardia and/or need for positive pressure ventilation).

Safety measures: overall mortality; adverse events including co-morbidities of prematurity (acquired sepsis/pneumonia, necrotizing enterocolitis, bronchopulmonary dysplasia); growth (weight, length, and head circumference); significant clinical laboratory changes, and trough blood levels determined in a subset of at least 24 patients.

Study 4: Supraesophageal and airway complications associated with GERD; GERD signs and symptoms (e.g., vomiting/regurgitation; irritability); growth parameters (including weight and height/length); frequency, severity, and duration of aspiration and wheezing; compliance.

Study 5: Signs and symptoms of pediatric GERD, concomitant antacid consumption, physical well-being.

DRUG INFORMATION:

The studies described above should use an age-appropriate formulation of pantoprazole sodium. The relative bioavailability of these age-appropriate formulations should be determined and compared with the marketed formulations of pantoprazole sodium. Full study reports of any relative bioavailability studies should be submitted to the Agency. If age-appropriate formulations cannot be developed, complete documentation of your attempts and a detailed explanation of why the attempts were unsuccessful should be submitted. Under these circumstances other formulations can be used, if they are standardized, palatable, and shown in adults to be of acceptable relative bioavailability (compared with the marketed products).

STATISTICAL INFORMATION:

In each pharmacokinetic study, the pharmacokinetic parameters of pantoprazole sodium may be summarized using descriptive statistics. In each pharmacodynamic study, the pharmacodynamic analysis will include an assessment of the time course of change of intragastric or intraesophageal pH, along with an assessment of dose effects. Mean ($\pm$SD) and median AUC for hydrogen ion secretion over the evaluation period will be calculated and compared among the doses.

In Study 2, treatment regimens will be compared with regard to change in obstructive apnea using appropriate statistical methods. A sufficient number of patients will complete the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided $p \leq 0.05$).

In Study 4, treatment regimens will be compared with regard to clinical outcomes using appropriate statistical methods. A sufficient number of patients will complete the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided $p \leq 0.05$).

In Studies 2, 4, and 5 treatment regimens will be compared with regard to change in growth parameters, symptoms and other responses.

ADDITIONAL INFORMATION NEEDED:

Perform a thorough review of the medical literature on the use of pantoprazole sodium in pediatric patients and provide a critical analysis and summary.

In addition, you should address the use of pantoprazole sodium for the maintenance of healing of erosive esophagitis and *H. pylori* eradication in pediatric patients. This can be done by: 1) reviewing, assessing, and submitting the available published information on the use of pantoprazole sodium in these patient populations and considering whether for the pediatric population or any portion of the pediatric population the disease and drug effects in those pediatric patients are similar as in adults or 2) a prospectively designed randomized, controlled clinical trial in this/these indication(s).

The Agency is concerned that pediatric patients may show progression of cellular changes beyond the proliferative changes in enterochromaffin-like (ECL) cells observed in adults who have used pantoprazole sodium. Before initiating the above clinical studies, please provide nonclinical and clinical data that helps to determine whether pediatric patients are at any increased risk with respect to these proliferative changes in gastric ECL cells.

To further assess the carcinogenicity potential of pantoprazole sodium and its safety for human use, perform a 26-week carcinogenicity study heterozygous p53 (+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose ranging study in C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints.

Before pediatric studies are initiated, you must document that pediatric patients are not at increased risk due to the carcinogenicity potential of pantoprazole sodium. Also, the Agency must have reviewed the submitted data and concurred with that assessment. We are available to discuss your plan for providing the requested data and studies that will be conducted.

LABELING THAT MAY RESULT FROM THE STUDIES:

Appropriate sections of the label may be changed to incorporate the findings of the studies.

FORMAT OF REPORTS TO BE SUBMITTED:

Full study reports (not previously submitted) should be submitted to the Agency addressing the issues outlined in this request, with full analysis, assessment, and interpretation.

TIMEFRAME FOR SUBMITTING REPORTS OF THE STUDIES:

Reports of the above studies must be submitted to the Agency on or before December 31, 2005.

Please keep in mind that pediatric exclusivity only attaches to existing patent protection or exclusivity that has not expired at the time you submit your reports of the studies in response to this Written Request.

Please submit protocols for the above studies to an investigational new drug application (IND) and clearly mark your submission, **"PEDIATRIC PROTOCOL SUBMITTED FOR PEDIATRIC EXCLUSIVITY STUDY**" in large font, bolded type at the beginning of the cover letter of the submission. Please notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Please clearly mark your submission, **"PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIE**S" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must be submitted as a supplement to an approved NDA with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS - PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED"** in large

font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request must be clearly marked **"PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits in the pediatric population.

If you have any questions, call Cheryl Perry, Regulatory Health Project Manager, at (301) 827-7475.

Sincerely,

Victor F. C. Raczkowski, M.D., M.S.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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

/s/

Victor Raczkowski
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Written request for pantoprazole sodium