



## DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

### WRITTEN REQUEST – AMENDMENT # 4

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NDA 20-406  
NDA 21-281  
NDA 21-428

TAP Pharmaceutical Products Inc.  
Attention: Donna Helms  
Director, Regulatory Affairs  
675 North Field Drive  
Lake Forest, IL 60045

Dear Ms. Helms:

Please refer to your correspondences dated July 23, 2004 and October 12, 2004, requesting changes to FDA's August 26, 1999, December 31, 2001, June 18, December 18, 2002, June 3, 2003, May 7, and December 14, 2004 original and amended Written Requests for pediatric studies for lansoprazole, specifically, Prevacid® (lansoprazole) Delayed-Release Capsules, Prevacid® (lansoprazole) For Delayed-Release Oral Suspension, and Prevacid® SoluTab (lansoprazole) Delayed-Release Orally Disintegrating Tablet.

We have reviewed your proposed changes and are amending studies 1 thru 4 of the Written Request as well as combining all of your previously issued Written Requests into one consolidated document. In order to communicate clearly the changes we have made, we are including a clean version (see attachment 1) and a marked-up version (see attachment 2) of your Written Request. Please note that these changes are denoted by underlined and ~~struck through~~ text in the marked-up version. All terms stated in our Written Request issued on August 26, 1999, and as amended on December 31, 2001, June 18, December 18, 2002, June 3, 2003, May 7, and December 14, 2004, remain the same.

Reports of the studies that meet the terms of the Written Requests dated August 26, 1999, December 31, 2001, June 18, and December 18, 2002, as amended by this letter, must be submitted to the Agency on or before December 31, 2008, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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. 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 STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission.

Submit reports of the studies as a supplement to an approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, 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. In addition, send a copy of the cover letter of your submission, via

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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, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request

**“PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES”** in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

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 to the pediatric population.

If you have any questions, call Melissa Hancock Furness, Regulatory Project Manager, at (301) 827-7450.

Sincerely,

*{See appended electronic signature page}*

Julie Beitz, M.D.  
Deputy Director  
Office of Drug Evaluation III  
Center for Drug Evaluation and Research

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## **ATTACHMENT 1**

### **THE PREVACID® (LANSOPRAZOLE) PEDIATRIC WRITTEN REQUEST:**

To obtain needed information about the use of lansoprazole (Prevacid®), 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 following studies:

#### **Types of Studies:**

As used in this Written Request, a *preterm infant* is an infant who has completed less than 37 complete weeks of gestation. A *term infant* is an infant that has completed 37-42 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.

#### **STUDY 1: PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD), EFFICACY, AND SAFETY STUDY IN PEDIATRIC PATIENTS LESS THAN 12 MONTHS OF AGE**

##### **PART A: Pharmacokinetic, Pharmacodynamic, and Safety Evaluation of Neonates and of Preterm Infants With a Corrected Age Less Than 44 Weeks**

**Inclusion Criteria:** To be included in Part A of this study, infants will: (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery at the time of enrollment in the study, (b) be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (c) 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 (d) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in this part of the study.

You may either do this in 2 study phases or a combined study as indicated below.

#### **Individual Phases: Two Separate Studies**

**Phase 1 (single dose):** This will be a randomized, single-dose pharmacokinetic and safety evaluation of at least two dose-levels of lansoprazole. 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 phase 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.

**Phase 2 (repeated dose):** This will be a repeated dose PK, PD, and safety evaluation of lansoprazole. The dose level(s) and frequency of dosing used in this phase of the study will be selected based on results from Phase 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. The duration of exposure should be 5-7 days. At least 12 patients per treatment group will complete this phase 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 patients who require tube placement or pH monitoring for clinical management. These patients may be

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already enrolled in the study here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

### **Combined: Phase 1 and Phase 2 can be combined into one study**

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two doses of lansoprazole. The duration of exposure should be 5-7 days. 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 dose group) will complete this 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 after single and repeated doses in at least six of patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

## **PART B: Pharmacokinetic, Pharmacodynamic and Safety Evaluation in Pediatric Patients 1 to 11 Months of Age**

**Inclusion Criteria:** To be included in Part B of this study, infants will (a) be 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 this part of the study.

You may either do this in 2 study phases or a combined study as indicated below.

### **Individual Phases: Two Separate Studies**

**Phase 1 (single dose):** This will be a randomized, single-dose pharmacokinetic and safety evaluation of at least two dose-levels of lansoprazole. 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 phase of the study if a standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

**Phase 2 (repeated dose):** This will be a repeated dose PK, PD, and safety evaluation of lansoprazole in pediatric patients. This phase will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of lansoprazole. The dose level(s) and frequency of dosing used in this phase of the study will be selected based on results from Phase 1. The duration of exposure should be 5-7 days. 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 patients who require tube placement or pH monitoring for clinical management. The patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

### **Combined: Phase 1 and Phase 2 can be combined into one study**

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two doses of lansoprazole. 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 dose group) will complete this 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 after single and repeated

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doses in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

## PART C: Efficacy and Safety Evaluation of Pediatric Patients 1 to 11 Months of Age

**Inclusion Criteria:** To be included in Part C of 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 this part of the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from this part of 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 either be a multicenter, treatment-withdrawal evaluation or a parallel group placebo controlled study of the efficacy and safety of lansoprazole.

### Treatment Withdrawal Evaluation

**Design:** This will be a multicenter, treatment withdrawal evaluation of the efficacy and safety of lansoprazole in which treatment withdrawal is randomized, double-blind and placebo controlled. The dosage(s) of lansoprazole used in this part of the study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Part B of this study, 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 this part of 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 lansoprazole in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by lansoprazole is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this phase 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 lansoprazole 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.

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**Placebo-Controlled Design:** Alternatively, a parallel group placebo controlled design may be used. This design will also consider dosing, randomization, stratification, concomitant medications, and other study elements, as mentioned above for the treatment withdrawal design.

**STUDY 2: CLINICAL OUTCOME, PHARMACOKINETIC, AND PHARMACODYNAMIC STUDY OF AGE-APPROPRIATE FORMULATION(S) OF LANSOPRAZOLE IN PEDIATRIC PATIENTS WITH SYMPTOMATIC AND/OR ENDOSCOPICALLY PROVEN GERD AGED 1 TO 11 YEARS INCLUSIVE:**  
multicenter, open-label, 8 to 12-week study in at least 60 patients.

**STUDY 3: PHARMACOKINETIC, PHARMACODYNAMIC, AND SYMPTOM ASSESSMENT STUDY OF LANSOPRAZOLE IN PEDIATRIC PATIENTS AGED 12 TO 17 YEARS INCLUSIVE:**  
multicenter, randomized, double-blind, 5-day study in at least 30 patients with symptomatic and/or endoscopically proven GERD per treatment group.

**STUDY 4: CLINICAL OUTCOME STUDY OF LANSOPRAZOLE IN PEDIATRIC PATIENTS AGED 12 TO 17 YEARS INCLUSIVE:**

multicenter, open-label, parallel group, 8 to 12-week study in at least 80 patients of both sexes with GERD symptoms for at least three months in whom gastrointestinal endoscopy has been performed.

Patients with non-erosive GERD will receive lansoprazole 15 mg daily and those with erosive esophagitis will receive lansoprazole 30 mg daily.

**Indication to Be Studied:**

Treatment of gastroesophageal reflux disease.

**Objectives:**

**Study 1:**

Parts A and B:

- (a) To characterize the pharmacokinetic/pharmacodynamic profile of single and repeated doses of lansoprazole in neonates, pre-term infants, with a corrected age less than 44 weeks, and pediatric patients 1-11 months 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 lansoprazole.

Part C:

- (a) To obtain efficacy data for lansoprazole in pediatric patients 1 to 11 months of age.
- (b) To assess the safety of lansoprazole in pediatric patients 1 to 11 months of age.

**Study 2:**

To assess the PK/PD/safety profile and symptoms response to lansoprazole in pediatric patients aged 1 to 11 years.

**Study 3:**

To assess the PK/PD/safety profile of two dose levels (15 and 30 mg once a day) of lansoprazole in pediatric patients aged 12 to 17 years.

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#### **Study 4:**

- (1) To assess the effects of two dose levels (15 and 30 mg once a day) of lansoprazole on GERD-related manifestations and/or on the healing of mucosal lesions;
- (2) To evaluate the safety of lansoprazole in pediatric patients aged 12 to 17 years.

#### **Age group in which studies will be performed:**

Study 1: Age less than 12 months.

Study 2: Ages 1 to 11 years inclusive.

Study 3: Ages 12 to 17 years inclusive.

Study 4: Ages 12 to 17 years inclusive.

#### **Evaluations and Endpoints:**

##### **Study 1:**

**Pharmacokinetics:** In the PK parts of the study, appropriate pharmacokinetic parameters will be assessed (e.g., AUC, apparent clearance,  $T_{max}$ ,  $t^{1/2}$ , apparent volume of distribution,  $C_{max}$  and others as appropriate). Pharmacokinetic characteristics following repeated dose will be evaluated and compared to a single dose.

**Pharmacodynamics:** In the PD parts of the study, appropriate pharmacodynamic parameters will be assessed (e.g., AUC of the gastric H<sup>+</sup> 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 lansoprazole dose.

**Safety and Tolerability:** 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.

#### **Other clinical outcomes and endpoints:**

##### **Study 1**

**Part C:** 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; and compliance with study drug administration.

##### **Study 2**

Assessment of (1) AUC,  $C_{max}$ ,  $T_{max}$ , and  $t^{1/2}$ , and other pharmacokinetic parameters as appropriate; (2) pharmacodynamic parameters (e.g., 24 h intraesophageal and intragastric pH monitoring in all patients); and (3) symptoms.

##### **Study 3**

Assessment of: (1) AUC,  $C_{max}$ ,  $T_{max}$ , and  $t^{1/2}$ , and other pharmacokinetic parameters as appropriate and (2) pharmacodynamic parameters (e.g., 24 h intraesophageal and intragastric pH monitoring in all patients).

##### **Study 4**

Primary: Relief of GERD-related symptoms or manifestations, as measured by the patient's daily diary card (as documented by the patient or caregiver, as appropriate).

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Secondary: Healing of mucosal lesions and/or relief of symptoms after 8 to 12 weeks of treatment with lansoprazole.

**Drug Information:**

Develop age-appropriate formulation(s) of lansoprazole and use them in the single and multiple-dose studies. The relative bioavailability of these age-appropriate formulations, as compared to marketed formulations of Prevacid Delayed-Release Capsules (15 and 30 mg), must be determined. The full study reports of these relative bioavailability studies must be submitted to the Agency. If age-appropriate formulation(s) cannot be developed, you will need to provide complete documentation of your attempts along with justification as to why this was not possible as part of your letter requesting an amendment to this written request. Marketed formulations of Prevacid Delayed-Release Capsules (15 and 30 mg) may be administered to pediatric patients older than one year given the variety of foods that the capsule contents are approved to mix with.

**Safety evaluations and procedures:**

In each study, the evaluation of safety should 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 should be made throughout each subject's study participation.

In all studies, patients should be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure should be fully documented, as should the use of any rescue medications.

**Statistical Information:**

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

In Study 1, Part C, treatment regimens will be compared with regard to clinical outcomes using appropriate statistical methods. A sufficient number of patients will complete this part of the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided  $p \leq 0.05$ ). Additionally, treatment regimens will be compared with regard to change in growth parameters, symptoms, and other responses.

In Study 3, changes in severity and frequency of GERD-related manifestations should be compared with baseline observations.

**Additional Information Needed:**

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

In addition, you should address the use of lansoprazole for the treatment of duodenal ulcers and benign gastric ulcers; for the eradication of *H. pylori*; and for the maintenance of healed erosive esophagitis in pediatric patients. This can be done by: (1) reviewing, assessing, and submitting the available published information on the use of lansoprazole 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) completing a prospectively designed, randomized, controlled clinical trial in these indications.

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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 lansoprazole. Experimentally, proton pump inhibitors have been shown to be genotoxic (mutagenic, clastogenic) and carcinogenic. The experimental carcinogenicity was expressed not only by development of carcinoids, but by the neoplastic growth of other gastrointestinal and systemic tumors in animals.

To address this concern, the following studies must be performed with lansoprazole:

- A 4-week repeated dose toxicity study in neonatal rats and
- A 90-day repeated dose toxicity study in neonatal dogs

In these nonclinical studies, gastric ECL cell morphology must be specifically evaluated and toxicokinetic measurements must be made. Special attention should be paid to the developmental parameters in these neonates. The study designs must also include three-month recovery groups. These nonclinical studies must be performed before clinical pediatric studies in patients less than 1 year of age are conducted (Parts A, B  and C  of Study 1). These nonclinical studies may be performed concurrently with clinical pediatric studies in patients 1 year of age and older (Studies 2, 3, and 4).

To further assess the carcinogenicity potential of lansoprazole and its safety for human use, perform a minimum 26-week carcinogenicity study in 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. This study in transgenic mice may be performed concurrently with clinical pediatric studies of lansoprazole.

In addition, provide a critical summary of clinical data (e.g., from the medical literature) that helps to determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric ECL cells.

Complete study reports for these nonclinical studies and the summary of clinical data must be submitted to FDA on or before the date specified below in the section titled "**Timeframe for Submitting Reports of the Studies.**"

**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:**

Please submit full study reports — addressing the issues outlined in this request with full analysis, assessment, and interpretation — that have not been submitted to the Agency. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

**Timeframe for submitting study reports:**

Reports of the above cited studies must be submitted to the Agency on or before December 31, 2008. Please keep in mind that pediatric exclusivity attaches only 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.

**Response to Written Request:**

As per the Best Pharmaceuticals for Children Act (BPCA), Section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies should be submitted as a New Drug Application (NDA) or as a supplement to your 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.

In accordance with section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

- (1) the type of response to the Written Request (complete or partial);
- (2) the status of the supplement (withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e., approval, approvable, not approvable); or
- (4) the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Clearly mark submissions of proposed changes to this request "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. We will notify you in writing if we agree to any changes to this Written Request.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for

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Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

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## **ATTACHMENT 2**

### **THE PREVACID® (LANSOPRAZOLE) PEDIATRIC WRITTEN REQUEST:**

To obtain needed information about the use of lansoprazole (Prevacid®), 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 following studies:

#### **Types of Studies:**

As used in this Written Request, a *preterm infant* is an infant who has completed less than 387 complete weeks of gestation. A *term infant* is an infant that has completed 387-42 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.

#### **STUDY 1: PHARMACOKINETIC (PK), PHARMACODYNAMIC (PD), EFFICACY, AND SAFETY STUDY IN PEDIATRIC PATIENTS LESS THAN 12 MONTHS OF AGE**

##### **PART A: Pharmacokinetic, Pharmacodynamic, and Safety Evaluation of Neonates and of Preterm Infants With a Corrected Age Less Than 44 Weeks**

**Inclusion Criteria:** To be included in Part A of this study, infants will: (a) be monitored patients admitted to a newborn intensive care unit (NICU) or special care nursery at the time of enrollment in the study, (b) have evidence of obstructive apnea by pneumographic monitoring (e) be considered candidates for acid suppressive therapy to treat a presumptive diagnosis of GERD, (c) (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 (d) (e) have a body weight of at least 800 grams. Patients of both sexes will be enrolled in this part of the study.

You may either do this in 2 study phases or a combined study as indicated below.

#### **Individual Phases: Two Separate Studies**

**Phase 1 (single dose):** This will be a randomized, single-dose pharmacokinetic and safety evaluation of at least two dose-levels of lansoprazole. 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 phase 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. An open-label design is acceptable.

**Phase 2 (repeated dose):** This will be a repeated dose PK, PD, and safety evaluation of lansoprazole. The dose level(s) and frequency of dosing used in this phase of the study will be selected based on results from Phase 1. If more than one dosage regimen is evaluated, patients will be randomly allocated to treatment groups in approximately equal proportions. The duration of exposure should be 5-7 days. At least 12 patients per treatment group will complete this phase 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.

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These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

### **Combined: Phase 1 and Phase 2 can be combined into one study**

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two doses of lansoprazole. The duration of exposure should be 5-7 days. 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 dose group) will complete this 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 after single and repeated doses in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

### **PART B: Efficacy and Safety Evaluation of Neonates and of Preterm Infants With a Corrected Age of Less Than 44 Weeks**

**Inclusion Criteria:** To be included in Part B of this study, patients must meet the same inclusion criteria specified above for Part A.

**Design:** This will be a multicenter treatment withdrawal evaluation of the efficacy and safety of lansoprazole in which treatment withdrawal is randomized, double blind, and placebo controlled. The dosage(s) of lansoprazole used in this part of the study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Part A of this study 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 this part of 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 lansoprazole in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by lansoprazole is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this phase 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 lansoprazole 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/badycardia 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.

### **PART B-C: Pharmacokinetic, Pharmacodynamic and Safety Evaluation in Pediatric Patients 1 to 11 Months of Age**

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**Inclusion Criteria:** To be included in Part **B-C** of 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 this part of the study.

You may either do this in 2 study phases or a combined study as indicated below.

### Individual Phases: Two Separate Studies

**Phase 1 (single dose):** This will be a randomized, single-dose pharmacokinetic and safety evaluation of at least two dose-levels of lansoprazole. 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 phase of the study if a standard PK approach is used. Alternatively, a population PK approach may be used. An open-label design is acceptable.

**Phase 2 (repeated dose):** This will be a repeated dose PK, PD, and safety evaluation of lansoprazole in pediatric patients. This phase will be designed to characterize the change in gastric and/or esophageal pH after repeated doses of lansoprazole. The dose level(s) and frequency of dosing used in this phase of the study will be selected based on results from Phase 1. The duration of exposure should be 5-7 days. 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. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

### Combined: Phase 1 and Phase 2 can be combined into one study

This will be a randomized, single and repeated dose pharmacokinetic, pharmacodynamic, and safety evaluation of at least two doses of lansoprazole. The duration of exposure should be 5-7 days. 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 dose group) will complete this 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 after single and repeated doses in at least six patients who require tube placement or pH monitoring for clinical management. These patients may be already enrolled in the study described here, or other patients not related to the protocol and in whom such measurements would be valid. An open-label design is acceptable.

### **PART C-D: Efficacy and Safety Evaluation of Pediatric Patients 1 to 11 Months of Age**

**Inclusion Criteria:** To be included in Part **C-D** of 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 this part of the study. Patients with histories of acute life-threatening events due to manifestations of GERD will be excluded from this part of 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

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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 either be a multicenter, treatment-withdrawal evaluation or a parallel group placebo controlled study of the efficacy and safety of lansoprazole.

### **Treatment Withdrawal Evaluation**

**Design:** This will be a multicenter, treatment withdrawal evaluation of the efficacy and safety of lansoprazole in which treatment withdrawal is randomized, double-blind and placebo controlled. The dosage(s) of lansoprazole used in this part of the study will be selected as dosages likely to be therapeutically effective and safe based on data obtained from Part B C of this study, 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 this part of 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 lansoprazole in this phase. Treatment in this phase will be of sufficient duration to ensure that gastric acid suppression by lansoprazole is at steady state. An open-label design is acceptable. The reasons for any patient discontinuations during this phase 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 lansoprazole 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.

**Placebo-Controlled Design:** Alternatively, a parallel group placebo controlled design may be used. This design will also consider dosing, randomization, stratification, concomitant medications, and other study elements, as mentioned above for the treatment withdrawal design.

STUDY 2: CLINICAL OUTCOME, PHARMACOKINETIC, AND PHARMACODYNAMIC STUDY OF AGE-APPROPRIATE FORMULATION(S) OF LANSOPRAZOLE IN PEDIATRIC PATIENTS WITH SYMPTOMATIC AND/OR ENDOSCOPICALLY PROVEN GERD AGED 1 TO 11 YEARS INCLUSIVE: multicenter, open-label, 8 to 12-week study in at least 60 patients.

STUDY 3: PHARMACOKINETIC, PHARMACODYNAMIC, AND SYMPTOM ASSESSMENT STUDY OF LANSOPRAZOLE IN PEDIATRIC PATIENTS AGED 12 TO 17 YEARS INCLUSIVE:

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multicenter, randomized, double-blind, 5-day study in at least 30 patients with symptomatic and/or endoscopically proven GERD per treatment group.

#### STUDY 4: CLINICAL OUTCOME STUDY OF LANSOPRAZOLE IN PEDIATRIC PATIENTS AGED 12 TO 17 YEARS INCLUSIVE:

multicenter, open-label, randomized, parallel group, 8 to 12-week study in at least 80 patients of both sexes with GERD symptoms for at least three months in whom gastrointestinal endoscopy has been performed.

Patients with non-erosive GERD will receive lansoprazole 15 mg daily and those with erosive esophagitis will receive lansoprazole 30 mg daily.

##### **Indication to Be Studied:**

Treatment of gastroesophageal reflux disease.

##### **Objectives:**

###### **Study 1:**

Parts A and B C:

- (a) To characterize the pharmacokinetic/pharmacodynamic profile of single and repeated doses of lansoprazole in neonates, pre-term infants, with a corrected age less than 44 weeks, and pediatric patients 1-11 months 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 lansoprazole.

###### Part B:

- ~~(a) To obtain efficacy data as measured by obstructive apnea for lansoprazole in preterm infants and neonates.~~  
~~(b) To assess the safety of lansoprazole in preterm infants and neonates.~~

###### Part C D:

- (a) To obtain efficacy data for lansoprazole in pediatric patients 1 to 11 months of age.  
(b) To assess the safety of lansoprazole in pediatric patients 1 to 11 months of age.

###### **Study 2:**

To assess the PK/PD/safety profile and symptoms response to lansoprazole in pediatric patients aged 1 to 11 years.

###### **Study 3:**

To assess the PK/PD/safety profile of two dose levels (15 and 30 mg once a day) of lansoprazole in pediatric patients aged 12 to 17 years.

###### **Study 4:**

- (1) To assess the effects of two dose levels (15 and 30 mg once a day) of lansoprazole on GERD-related manifestations and/or on the healing of mucosal lesions;  
(2) To evaluate the safety of lansoprazole in pediatric patients aged 12 to 17 years.

##### **Age group in which studies will be performed:**

Study 1: Age less than 12 months.

Study 2: Ages 1 to 11 years inclusive.

Study 3: Ages 12 to 17 years inclusive.

Study 4: Ages 12 to 17 years inclusive.

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## Evaluations and Endpoints:

### Study 1:

**Pharmacokinetics:** In the PK parts of the study, appropriate pharmacokinetic parameters will be assessed ~~for both the single and repeated dose portions of the study~~ (e.g., AUC, apparent clearance,  $T_{max}$ ,  $T_{1/2}$ , apparent volume of distribution,  $C_{max}$  and others as appropriate). Pharmacokinetic characteristics following repeated dose will be evaluated and compared to a single dose.

**Pharmacodynamics:** In the PD parts of the study, appropriate pharmacodynamic parameters will be assessed (e.g., AUC of the gastric H<sup>+</sup> 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 lansoprazole dose.

**Safety and Tolerability:** 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 Part B and Part D of the study will undergo follow up developmental, growth, and safety assessments 6 and 12 months after enrollment.

## Other clinical outcomes and endpoints:

### Study 1

Part A: Apnea and bradycardia will be assessed concurrent to pHmetry.

Part B: 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<sub>2</sub> 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.

Part C D: 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; and compliance with study drug administration.

### Study 2

Assessment of (1) AUC,  $C_{max}$ ,  $T_{max}$ , and  $t_{1/2}$ , and other pharmacokinetic parameters as appropriate; (2) pharmacodynamic parameters (e.g., 24 h intraesophageal and intragastric pH monitoring in all patients); and (e) (3) symptoms.

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### **Study 3**

Assessment of: (1) AUC, C<sub>max</sub>, T<sub>max</sub>, and t<sub>1/2</sub>, and other pharmacokinetic parameters as appropriate and (2) pharmacodynamic parameters (e.g., 24 h intraesophageal and intragastric pH monitoring in all patients).

### **Study 4**

Primary: Relief of GERD-related symptoms or manifestations, as measured by the patient's daily diary card (as documented by the patient or caregiver, as appropriate).

Secondary: Healing of mucosal lesions and/or relief of symptoms after 8 to 12 weeks of treatment with lansoprazole.

### **Drug Information:**

Develop age-appropriate formulation(s) of lansoprazole and use them in the single and multiple-dose studies. The relative bioavailability of these age-appropriate formulations, as compared to marketed formulations of Prevacid Delayed-Release Capsules (15 and 30 mg), should must be determined. The full study reports of these relative bioavailability bioavailability studies should must be submitted to the Agency. If age-appropriate formulation(s) cannot be developed, you will need to provide complete documentation of your attempts along with justification as to why this was not possible as part of your letter requesting an amendment to this written request. Marketed formulations of Prevacid Delayed-Release Capsules (15 and 30 mg) may be administered to pediatric patients who are able to swallow them older than one year given the variety of foods that the capsule contents are approved to mix with.

### **Drug Specific Safety concerns:**

#### **Study 1:**

Individuals, such as caregivers, who will be making assessments of apnea and/or bradycardia should be trained appropriately in apnea/bradycardia monitoring procedures, particularly in the use of apnea and/or bradycardia monitors. The nature and extent of this training should be fully documented.

Provisions should be taken to assure that patients are adequately hydrated and have sufficient caloric intake during times that they are NPO. Patients should be carefully monitored for apnea, bradycardia, aspiration, nausea, and vomiting that may be more commonly seen in young pediatric patients with GERD, as well as for adverse reactions, such as those frequently seen with lansoprazole (e.g., headache, diarrhea, and abdominal discomfort/pain).

### **Safety evaluations and procedures:**

In each study, the evaluation of safety should 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 should be made throughout each subject's study participation.

In all studies, patients should be followed until adverse events have been adequately resolved. Withdrawals from the studies because of serious adverse events or treatment failure should be fully documented, as should the use of any rescue medications.

### **Statistical Information:**

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

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~~In Study 1, Part B, treatment regimens will be compared with regard to change in obstructive apnea using appropriate statistical methods. A sufficient number of patients will complete this part of 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 1, Part C D, treatment regimens will be compared with regard to clinical outcomes using appropriate statistical methods. A sufficient number of patients will complete this part of the study to ensure at least 80% statistical power to detect a clinically meaningful treatment effect at conventional statistical significance (i.e., two-sided  $p \leq 0.05$ ). Additionally, treatment regimens will be compared with regard to change in growth parameters, symptoms, and other responses.

~~In Study 1, Parts B and D, treatment regimens will be compared with regard to change in growth parameters, symptoms and other responses.~~

~~In Study 3, changes in severity and frequency of GERD-related manifestations should be compared with baseline observations. The proportion of patients with mucosal lesions at baseline who have healed at 4 weeks should be compared to an appropriate and relevant historical control. The adequacy and relevance of the historical control that is used should be fully documented.~~

#### **Additional Information Needed:**

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

In addition, you should address the use of lansoprazole for treating duodenal ulcer, benign gastric ulcer, and *H. pylori* infection and for maintenance of healing of the treatment of duodenal ulcers and benign gastric ulcers; for the eradication of *H. pylori*; and for the maintenance of healed erosive esophagitis in pediatric patients. This can be done by: (1) reviewing, assessing, and submitting the available published information on the use of lansoprazole 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) completing a prospectively designed, randomized, controlled clinical trial in these indications.

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 lansoprazole. ~~Before initiating the above clinical studies, please provide nonclinical and clinical data that help to determine whether pediatric patients are at any increased risk with respect to these proliferative changes in gastric ECL cells. Experimentally, proton pump inhibitors have been shown to be genotoxic (mutagenic, clastogenic) and carcinogenic. The experimental carcinogenicity was expressed not only by development of carcinoids, but by the neoplastic growth of other gastrointestinal and systemic tumors in animals.~~

To address this concern, the following studies must be performed with lansoprazole:

- A 4-week repeated dose toxicity study in neonatal rats and
- A 90-day repeated dose toxicity study in neonatal dogs

In these nonclinical studies, gastric ECL cell morphology must be specifically evaluated and toxicokinetic measurements must be made. Special attention should be paid to the developmental parameters in these neonates. The study designs must also include three-month recovery groups. These nonclinical studies must be performed before clinical pediatric studies in patients less than 1 year of age are conducted (Parts A, B  and C  of Study 1). These nonclinical studies may be performed concurrently with clinical pediatric studies in patients 1 year of age and older (Studies 2, 3, and 4).

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

~~If approved for pediatric use, a registry should be established for long term follow up of pediatric patients who have received lansoprazole. We will be available to discuss the design of such a registry.~~

To further assess the carcinogenicity potential of lansoprazole and its safety for human use, perform a minimum 26-week carcinogenicity study in 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. This study in transgenic mice may be performed concurrently with clinical pediatric studies of lansoprazole.

In addition, provide a critical summary of clinical data (e.g., from the medical literature) that helps to determine whether pediatric patients are at any increased risk with respect to proliferative changes in gastric ECL cells.

Complete study reports for these nonclinical studies and the summary of clinical data must be submitted to FDA on or before the date specified below in the section titled "Timeframe for Submitting Reports of the Studies."

#### **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:**

Please submit full study reports (~~that have not previously been submitted~~) to the Agency — addressing the issues outlined in this request with full analysis, assessment, and interpretation ~~— that have not been submitted to the Agency. In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the studies must be categorized using one of the following designations for race: American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.~~

#### **Timeframe for submitting study reports:**

Reports of the above cited studies ~~that meet the terms of the Written Request dated August 26, 1999, as amended by this letter,~~ must be submitted to the Agency on or before December 31, 2005 2008. ~~in order to possibly qualify for pediatric exclusivity extension under Section 505 of the Act.~~ Please keep in mind that pediatric exclusivity attaches only extends to existing patent protection or exclusivity that has not expired ~~or been previously extended~~ at the time you submit your reports of the studies in response to this Written Request.

#### **Response to Written Request:**

As per the Best Pharmaceuticals for Children Act (BPCA), Section 4(A), within 180 days of receipt of this Written Request you must notify the Agency as to your intention to act on the Written Request. If you agree to the request then you must indicate when the pediatric studies will be initiated.

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. Notify us as soon as possible if you wish to enter into a written agreement by submitting a

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proposed written agreement. Clearly mark your submission "PROPOSED WRITTEN AGREEMENT FOR PEDIATRIC STUDIES" in large font, bolded type at the beginning of the cover letter of the submission.

Reports of the studies must should be submitted as a New Drug Application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are 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.

In accordance with section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request and filed by FDA, regardless of the following circumstances:

- (1) the type of response to the Written Request (complete or partial);
- (2) the status of the supplement (withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e., approval, approvable, not approvable); or
- (4) the exclusivity determination (i.e., granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at <http://www.fda.gov/cder/pediatric/Summaryreview.htm> and publish in the *Federal Register* a notification of availability.

If you wish to discuss any amendments to this Written Request, submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked Clearly mark submissions of proposed changes to this request "**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 will notify you in writing if we agree to any changes to this Written Request.

As required by the Food and Drug Modernization Act and the Best Pharmaceuticals for Children Act, you are also responsible for registering certain clinical trials involving your drug product in the Clinical Trials Data Bank (<http://clinicaltrials.gov> & <http://prsinfo.clinicaltrials.gov/>). If your drug is intended for the treatment of a serious or life-threatening disease or condition and you are conducting clinical trials to test its effectiveness, then you must register these trials in the Data Bank. Although not required, we encourage you to register effectiveness trials for non-serious diseases or conditions as well as non-effectiveness trials for all diseases or conditions, whether or not they are serious or life-threatening. Additional information on registering your clinical trials, including the required and optional data elements and the FDA Draft Guidance for Industry, "Information Program on Clinical Trials for Serious or Life-Threatening Diseases and Conditions," is available at the Protocol Registration System (PRS) Information Site <http://prsinfo.clinicaltrials.gov/>.

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Julie Beitz  
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