DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-406
NDA 21-281

TAP Pharmaceutical Products, Inc.
Attention: Ms. Betsy A. Brown
Associate Director, Regulatory Affairs
675 North Field Drive
Lake Forest, IL 60045

Dear Ms. Brown:

Reference is made to your correspondence dated July 5, 2000, requesting changes to FDA's August 26, 1999 Written Request for pediatric studies for lansoprazole.

We also refer to the Agency's letter issued August 8, 2000 stating that an amended Written Request would not be issued until the Agency had assimilated information and obtained external opinion regarding the study of neonates and infants for the treatment of gastroesophageal reflux disease (GERD).

The Division of Gastrointestinal and Coagulation Drugs has completed these steps. The Division has concluded that the course of 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 lansoprazole, 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 the amended written request, efficacy studies must be performed in pediatric patients less than one year of age as summarized below. To accommodate these studies, we are extending the timeframe for submitting study reports to December 31, 2005.

We have reviewed your proposed changes, and are amending the below listed sections of the Written Request. All other terms stated in our Written Request issued on August 26, 1999 remain the same.

DELETIONS FROM THE WRITTEN REQUEST ISSUED AUGUST 26, 1999

Delete Study 1 in its entirety from the Written Request issued August 26, 1999. Citations pertinent to Study 1 should be deleted from the following sections of that Written Request:

1. Types of studies
2. Objectives
3. Age group in which studies will be performed
4. Evaluations and Endpoints
5. Drug Specific Safety concerns
6. Statistical information

ADDITIONS TO THE WRITTEN REQUEST ISSUED AUGUST 26, 1999

[Note: For clarity, we have listed the modifications to the August 26, 1999 Written Request in a different font.]

The following amendments should be added to the Written Request issued August 26, 1999:

1. Under **"Types of studies**," replace the deletions with the following:

"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.

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, (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 this part of the study.

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. 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 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/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.

PART C: Pharmacokinetic, Pharmacodynamic And Safety Evaluation In Pediatric Patients 1 To 11 Months Of Age

Inclusion criteria: To be included in Part 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.

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 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. 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.

PART D: Efficacy And Safety Evaluation Of Pediatric Patients 1 To 11 Months Of Age

Inclusion criteria: To be included in Part 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 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 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 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."

2. Under "**Objectives**," replace the deletions with the following:

"Parts A and C:

(a) To characterize the pharmacokinetic/pharmacodynamic profile of single and repeated doses of lansoprazole 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 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."

3. Under "**Age group in which studies will be performed**," replace the deletions with the following:

"Study 1: Age less than 12 months"

4. Under "**Evaluations and Endpoints**," replace the deletions with the following:

"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 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 parts of the study, 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 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:

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_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.

Part 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; compliance."

5. Under "**Drug Specific Safety concerns**," deletions need not be replaced.

6. Under "**Statistical information**,":

(a) The following paragraph should be *retained*:

"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."

(b) Deletions should be replaced by the following:

"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 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 $p \leq 0.05$).

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

Reports of the 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, in order to possibly qualify for pediatric exclusivity extension under Section 505A of the Act.

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 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.

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, contact Cheryl Perry, Regulatory Health Project Manager, at (301) 827-7475.

Sincerely,

{See appended electronic signature page}

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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Amendment #1 for lansoprazole pediatric Written Request