HFD 104
Murphy

NDA 20-406

AUG 26 1999

TAP Holdings Inc.
Attention: Gary C. Magistrelli, Ph.D.
2355 Waukegan Road
Deerfield, IL 60015

Dear Dr. Magistrelli:

Reference is made to your Proposed Pediatric Study Request submitted on October 8, 1998 for Prevacid (lansoprazole) Delayed-Release Capsules.

To obtain needed pediatric information on lansoprazole, 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:

Study 1:

Part 1: Single- and repeated-dose pharmacokinetic, pharmacodynamic (PK/PD), and safety evaluation of age-appropriate formulation(s) of lansoprazole in at least 80 neonates and infants (0 to 12 months of age and ≥ 800 grams) with symptomatic and/or endoscopically proven gastroesophageal reflux disease (GERD).

a) Single-dose PK/PD safety evaluation. This will be a randomized, double-blind, placebo-controlled, dose-escalation study. Lansoprazole will be administered in single doses in at least three dose levels (in addition to placebo). At least five patients will complete one dose before any patients receive the next higher dose.

b) Repeated-dose PK/PD/safety evaluation. This will be a randomized double-blind, placebo-controlled study. The dose and regimen of lansoprazole should be selected based on data from the single-dose PK/PD/safety evaluation.

Part 2: Clinical outcome and safety evaluation of at least 80 neonates and infants (0 to 12 months of age and ≥ 800 grams) with symptomatic and/or endoscopically proven GERD. This will be a randomized, double-blind, placebo-controlled study of age-appropriate formulation(s) of lansoprazole administered over at least two months using the dosing regimen(s) determined likely to be therapeutically effective and safe, based on the PK/PD/safety data obtained in Part 1.

In both Parts 1 and 2, patients should be excluded if they have secondary causes for reflux symptoms or if they respond adequately to conservative measures (e.g., thickening of feedings, prone upright positioning).

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, 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.

Indication to be studied:
Treatment of gastroesophageal reflux disease.

Objectives:
Study 1:

Part 1: (1) To characterize the PK/PD profile of single doses of lansoprazole: (2) To characterize the PK/PD profile of lansoprazole following repeated doses and at steady state; (3) To collect information on the safety of single and repeated doses of lansoprazole in these pediatric subjects.

Part 2: (1) To evaluate the ability of lansoprazole to alleviate manifestations of GERD when administered over two months with appropriate monitoring; (2) To evaluate the safety of lansoprazole administered over at least two months.

Study 2:

To assess the PK/PD/safety profile and symptoms response to lansoprazole.

Study 3:

To assess the PK/PD/safety profile of two dose levels (15 and 30 mg once a day) of lansoprazole.

Study 4:

(1) To assess the effects 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.

Age group in which studies will be performed:

Study 1: Age 0-12 months. To be enrolled, patients should weigh at least 800 grams. In both Parts 1 and 2, the age distribution should be comparable among the treatment groups and the entire age range should be represented.

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:

Part 1:

a) Pharmacokinetics: For single-dose and multiple-dose pharmacokinetic evaluation, pharmacokinetic parameters measured should include AUC, apparent clearance, T_{max}, $t_{½}$, volume of distribution, C_{max} and others as appropriate. For single-dose studies, blood samples should be drawn at appropriate intervals for at least 12 h. For multiple-dose studies, blood samples should be drawn at appropriate intervals for ≥ 12 h following at least 3 to 4 days of test medication.

b) Pharmacodynamics: For single-dose and multiple-dose pharmacodynamic evaluation, pharmacodynamic parameters evaluated should include: (a) the AUC of the intragastric H^+ time profile; (b) the median and mean pH; (c) the percentage of time pH≥4; and (d) percentage of time pH≥3. These intraesophageal and intragastric pH measurements should be measured over at least a 12 h period after dosing. PD measurements should be made just prior to dosing and at appropriate intervals after dosing to encompass the duration of drug effect. For patients receiving repeated dosing, PD measurements should be made at baseline (i.e. before therapy) and after the final lansoprazole dose.

Gastric secretions should be collected at intervals during the first several hours after dosing (e.g. just prior to dosing and at 30-minute intervals up to 6 h after dosing). Measurements should be made of volume, pH, and hydrogen ion activity.

Part 2:
Growth parameters (including weight and height); GERD symptoms or manifestations (e.g. number of regurgitation episodes); and frequency, severity, and duration of aspiration, apnea and/or bradycardia. These parameters and patient compliance should be assessed at weekly clinic visits. Caretakers should have appropriate training on procedures for apnea and bradycardia (see "Drug specific safety concerns").

Study 2: Assessment of: (1) AUC, C_{max}, T_{max}, and $t_{½}$ and other pharmacokinetic parameters as appropriate; (2) pharmacodynamic parameters (e.g. 24 h intraesophageal and intragastric pH monitoring in all patients); and c) symptoms.

Study 3: Assessment of: (1) AUC, C_{max}, T_{max}, and $t_{½}$ 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 be determined. The full study reports of these relative bioavialability studies should 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.

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).

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, treatment regimens should be compared with regard to change in growth parameters and change in symptoms.

In Study 3, changes in the 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:
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 erosive esophagitis in pediatric patients. This can be done by: 1) reviewing, assessing, and submitting the available published information on lansoprazole use 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 these indications.

The Agency is concerned that pediatric patients may show progression of cellular changes beyond the proliferative changes in 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.

Before pediatric studies are initiated, you must document that pediatric patients are not at increased risk due to the carcinogenicity potential 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 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 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.

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.

Timeframe for submitting study reports:
Reports of the above studies must be submitted to the Agency on or before December 1, 2001. Please keep in mind that pediatric exclusivity only extends existing patent protection or exclusivity that has not expired or been previously extended at the time you submit your report of the study in response to this Written Request.

Please submit protocols for the above studies to your 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. 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.

Your study reports should 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 should 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 Maria R. Walsh, M.S., Regulatory Project Manager, at (301) 443-8017.

Sincerely yours,

VR /for VR

Victor F. C. Raczkowski, MD, MS
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20 406
IND [redacted]
HFD-180/Division file
HFD-180/PM/M.Walsh
HFD-180/L.Talarico
H.Gallo-Torres
K.Robie-Suh
HFD-870/J.Hunt
D.Lee
HFD-103/V.Raczkowski
HFD-600/Office of Generic Drugs
HFD 2/M.Lumpkin
HFD-104/D.Murphy
HFD-104/T.Hassall
Drafted by: M.Walsh 7/29/99
Initialed by: H.Gallo-Torres 7/29/99, 8/19/99
L.Talarico 8/3/99, 8/19/99
V.Raczkowski 8/5/99, 8/20/99
Pediatric Committee 8/25/99
Revised: M.Walsh 8/19/99, 8/23/99
Final: M.Walsh 8/25/99
filename: 20406908.pedswrittenrequest.doc

PEDIATRIC WRITTEN REQUEST LETTER
INFORMATION REQUEST (IR)