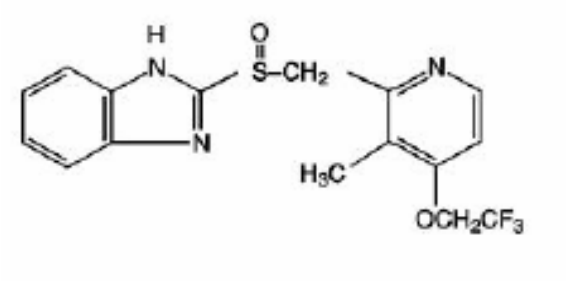
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF GASTROINTESTINAL & COAGULATION DRUG PRODUCTS

EXECUTIVE SUMMARY OF MEDICAL AND CLINICAL PHARMACOLOGY REVIEWS

PREVACID® (lansoprazole)



NDA#/Supplement#:	**20-406/S-057, 21-281/S-014, and 21-428/S-004**
Proposed Indications:	**The short-term treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old**
Drug Class:	Substituted benzimidazole proton pump inhibitor
Formulation and Route of administration:	Oral capsule
Proposed regimens:	Non-erosive GERD: 15 mg once daily for up to 8 weeks EE: 30 mg once daily for up to 8 weeks
Applicant:	TAP Pharmaceutical Products Inc.
Medical Reviewer:	Eric Brodsky, M.D.
Medical Team Leader:	Ruyi He, M.D.
Biopharmaceutics Reviewer:	Suliman Al-Fayoumi, Ph.D.
Biopharmaceutics Team Leader:	Suresh Doddapaneni, Ph.D.
Project Manager:	Melissa Furness
Date of Submission:	December 19, 2004
Review Date:	June 7, 2004

BACKGROUND

Lansoprazole is a proton pump inhibitor which was approved in the United States on May 10, 1995 for the treatment of a variety of acid-related esophageal, gastric, and duodenal disorders in adults. Lansoprazole inhibits gastric acid secretion by blocking the proton pump [(H+,K+)-ATPase enzyme system] at the secretory surface of the gastric parietal cell. Inhibition of the proton pump, the final step of stomach acid secretion, decreases intra-gastric acid concentration (increases intra-gastric pH). Based upon submitted adult and pediatric studies, lansoprazole was approved for the treatment of non-erosive gastro-esophageal reflux disease (GERD) and erosive esophagitis (EE) in adults and pediatric patients between the ages of 1 and 11 years old.

Lansoprazole is available by prescription in three oral formulations ─ prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) ─ and one intravenous formulation, prevacid I.V. (lansoprazole) for injection. All three oral formulations contain 15 mg or 30 mg of lansoprazole and the intravenous formulation contains 30 mg of lansoprazole.

TAP Pharmaceutical Products Inc. (TAP) provided two study reports, M97-640 and M00-158, to support the following new lansoprazole indications: the treatment of non-erosive GERD and EE in pediatric patients between ages 12 to 17 years old.

EXECUTIVE SUMMARY

1.0 RECOMMENDATIONS

1.1 Recommendations on Approvability

From a clinical perspective, prevacid® (lansoprazole) delayed-release capsules, prevacid® (lansoprazole) delayed-release oral suspension, and prevacid® (lansoprazole) delayed-release orally disintegrating tablets (solutab) are recommended for approval for the treatment of GERD (non-erosive GERD and EE) in pediatric patients between 12 and 17 years old.

1.2 Recommendation on Phase 4 Studies and/or Risk Management Steps

From a clinical perspective, this medical officer does not recommend phase 4 studies or risk management steps in pediatric GERD patients between 12 and 17 years old.

2.0. SUMMARY OF CLINICAL FINDINGS

2.1 Brief Overview of Clinical Program

TAP submitted two clinical study reports (Studies M97-640 and M00-158) to support the efficacy and safety of lansoprazole in the treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old. These studies, conducted exclusively in the United States, included a total of 150 pediatric GERD patients (between 12 and 17 years old) who all received upper endoscopies at baseline.

Study M97-640 was a randomized, double-blinded, multi-center (10 sites), pharmacokinetic (PK), and pharmacodynamic (PD) trial of lansoprazole in the treatment of pediatric GERD patients, ages 12 to 17 years old. Patients were randomized to two lansoprazole treatment groups: 15 mg/day (n = 32) or 30 mg/day (n = 31) for 5 consecutive days. The PK and PD of lansoprazole were assessed by plasma concentrations and 24-hour pH monitoring, respectively.

Study M00-158 was an uncontrolled, open-label, multi-center (20 sites) trial of lansoprazole in the treatment of GERD in pediatric patients, ages 12 to 17 years. Baseline upper endoscopies categorized pediatric GERD patients into two groups: non-erosive GERD (n = 64) and EE (n = 23). Non-erosive GERD patients received 15 mg of oral lansoprazole once daily for 8 weeks and EE patients received 30 mg of lansoprazole once daily for 8 weeks. EE patients with completely healed EE after 8 weeks of treatment were considered to have completed the therapy. In contrast, EE patients with unhealed EE after 8 weeks of treatment were treated with 30 mg of lansoprazole for an additional 4 weeks (12 weeks of total treatment).

The safety evaluation included assessment of the data from the two clinical studies and post-marketing data and literature reports in pediatric patients between 12 and 17 years old, who received lansoprazole.

2.2 Efficacy

Study M00-158: Sixty-four non-erosive GERD patients were treated with 15 mg of lansoprazole for 8 weeks and 23 EE patients were treated with 30 mg of lansoprazole for 8 to 12 weeks. The efficacy results are summarized below.

The co-primary endpoints were the change from baseline in the frequency and severity of GERD symptoms during the 8 week treatment period based on patient diary data. The patient diary results demonstrated an improvement in GERD symptoms during 8 weeks of lansoprazole treatment. The median percentage of days with GERD symptoms decreased from 88.9% to 33.3%. This was a statistically significant change ($p<0.001$). Furthermore, the average severity of GERD symptoms (0 = none; 1 = mild; 2 = moderate; 3 = severe; 4 = very severe) decreased from 1.6 (mild to moderate) to 0.5 (none to mild) and this was statistically significant ($p<0.001$). No placebo group was included in this trial.

The most important secondary endpoint was the proportion of patients who had endoscopically-documented complete esophageal healing at the week 8 and 12 visits. In this study, the appearance of the esophagus was scored by the TAP Esophagitis Grading Scale (developed by a committee of the sponsor's consultant gastroenterologists). Patients with normal appearing mucosa (grade 0) or mucosal edema, hyperemia and/or friability (grade 1) were classified to have non-erosive GERD. Patients with the appearance of at least one erosion/ulceration in the esophagus mucosa (grades 2, 3, or 4) were categorized to have EE.

Complete healing of EE was defined as the return of the esophageal mucosa to grade 0 or 1 (non-erosive GERD). Twenty-one of twenty-two (95.5%) EE patients were completely healed after 8 weeks of lansoprazole treatment. One patient remained unhealed after 12 weeks of lansoprazole treatment. However, all EE patients had grade 2 or 3 lesions; no EE patient had a grade 4 lesion in this study. These efficacy results support the proposed EE indication in pediatric patients between 12 and 17 years old.

Additional secondary endpoints were the change from baseline in the amount and frequency of antacid use during the first 8 weeks of lansoprazole treatment based on patient diary data. Rescue antacid use decreased from a median of 54.5% of the days during the pretreatment period to a median of 5.5% of the days during the lansoprazole treatment period ($p<0.001$). Furthermore, the amount of rescue antacid used, decreased from a median of 1.4 teaspoons/day during the baseline pretreatment period to a median of 0.2 teaspoons/day during the lansoprazole treatment period ($p<0.001$).

An additional secondary endpoint was the change from baseline in the severity of GERD symptoms at the week 8 visit based on investigator interviews. Investigators classified the patient's overall GERD symptoms on a 0 to 3 scale (none = 0, mild = 1, moderate = 2, and severe = 3). After 8 weeks of lansoprazole treatment, GERD patients who had severe (3) baseline symptoms, moderate (2) baseline symptoms, mild (1) baseline symptoms, improved their average GERD score to 0.67., 0.71, 0.71, respectively.

Study M97-640: The major endpoints evaluated were pharmacokinetic (C_{max} and AUC_{0-24}) and pharmacodynamic (after 5 days of lansoprazole treatment, the change from baseline in the mean 24 hour intra-gastric pH and the percentages of time that the pH exceeded 3 and 4) variables.

The results of this study demonstrated that the pharmacokinetics of lansoprazole are similar between the adolescents GERD patients in this study and previously observed healthy adult subjects. The mean dose-normalized C_{max} variables for the adolescent GERD patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 27.7, 33.5, and 27.5 ng/mL/mg, respectively. The mean dose-normalized AUC_{0-24} values for the adolescent patients who received 15 mg of lansoprazole, 30 mg of lansoprazole, and a historical population of healthy adult subjects were 67.8, 83.0, and 71.1 ng•hour/mL/mg, respectively.

For both lansoprazole treatments, compared to baseline measurements, the increase in the mean 24-hour intra-gastric pH and the percentages of time the mean intra-gastric pH were above 3 and 4 at the Day 5 Visit were statistically significant. The mean 24-hour intra-gastric pH for the adolescent GERD patients was 2.71 at baseline and 3.84 after 5 days of lansoprazole (15 mg/day), and was 2.81 at baseline and 3.89 after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 3 for the adolescent GERD patients was 26.7% at baseline and 58.9% after 5 days of lansoprazole (15 mg/day) and was 29.1% at baseline and 59.6% after 5 days of lansoprazole (30 mg/day). The percentage of time that the intra-gastric pH was over 4 for the adolescent GERD patients was 20.0% at baseline and 46.9% after 5 days of lansoprazole (15 mg/day) and was 20.4% at baseline and 48.9% after 5 days of lansoprazole (30 mg/day) .

Summary: The efficacy of lansoprazole in the proposed indication was demonstrated by similar lansoprazole pharmacokinetics in adolescent GERD patients compared to healthy adult subjects; by the increase in intra-gastric pH after 5 days of lansoprazole treatment in adolescent GERD patients; by the efficacy in the complete healing of EE after 8 weeks of lansoprazole treatment (95.5%) in adolescent GERD patients; and efficacy results of lansoprazole treatment in adult GERD patients.

2.3 Safety

All patients in Studies M97-640 and M00-158 who received at least one dose of lansoprazole were included in the safety analyses. The Integrated Summary of Safety (ISS) included data on 150 pediatric GERD patients between 12 and 17 years old. Of the total population, 64 (43%) and 81 (54%) patients received 1 to 9 days and 42 to 70 days of lansoprazole, respectively.

Five patients had serious adverse drug events [gastroenteritis, a suicide attempt, a torn hamstring muscle, and a collection of symptoms (including chest pain, abdominal pain, and increased cough)] that required hospitalization. All of these serious adverse events were not likely related to lansoprazole and all of these patients were able to continue in the trials.

Two patients withdrew from the lansoprazole trials due to adverse drug events (AEs). The investigators believed that both of the AEs were possibly related to the study drug. One patient discontinued lansoprazole treatment after 40 days of therapy because of mild dizziness and moderate vomiting. Another patient with a past medical history of asthma, allergies, and eosinophilic esophagitis, developed hives, peripheral edema, and a generalized papular rash after 3 days of lansoprazole treatment.

The most frequent experienced AEs that were possibly, probably, or definitely caused by lansoprazole treatment included headache, abdominal pain, nausea, and dizziness occurring in 4%, 3%, 2%, and 3% of patients, respectively. The AE profile in these pediatric patients resembled that of adult patients and pediatric patients (between ages 1 and 11) taking lansoprazole.

No hematology or chemistry serum test, urine test, or vital sign abnormality were likely due to lansoprazole therapy. Five patients in Study M00-158 developed serum gastrin levels over 200 pg/mL (normal gastrin range is 25 to 111 pg/mL) after 8 weeks of lansoprazole. Similar high serum levels of gastrin are seen in adults treated with lansoprazole. Hypergastrinemia is a well-documented effect of all the PPIs in adults. Furthermore, hypergastrinemia was documented in GERD studies in pediatric patients between ages 1 to 11 years old.

No drug interaction studies of lansoprazole were conducted in adolescents. Based on the known potential drug interactions of lansoprazole with theophylline, digoxin, phenobarbital, carbamazepine, and/or phenytoin in adults; similar precautions should be taken when these medications are given concomitantly with lansoprazole in adolescent patients.

2.4 Dosing

This medical officer recommends a lansoprazole dose of 15 mg once daily for 4 to 8 weeks for the treatment of non-erosive GERD and a lansoprazole dose of 30 mg once daily for 6 to 8 weeks for the treatment of EE in pediatric patients between the ages of 12 to 17 years old. The evidence for this dosing recommendation is from numerous GERD studies in adult patients and the two supportive pediatric studies submitted in these sNDAs.

Since the efficacy of non-erosive GERD and EE treatment with lansoprazole in adolescent patients is primarily based on the safety and efficacy of lansoprazole in adult patients, the pediatric regimen should be similar to the safe and effective adult regimen. The treatment of

non-erosive GERD in adults with lansoprazole for 2 weeks is less effective than 4 to 8 weeks of lansoprazole treatment. Similarly, the treatment of EE in adults with lansoprazole for 2 to 4 weeks is less effective than 6 to 8 weeks of lansoprazole treatment. Therefore, the adolescent dose of lansoprazole in the treatment of non-erosive GERD and EE should be at least 4 weeks and 6 weeks, respectively.

2.5 Special Populations

2.5.1 Gender: The total pediatric GERD population included 66 males and 84 females. A similar percentage of females and males experienced AEs (55% and 48%, respectively) in the two studies. There was no evidence that gender affected the development of AEs during treatment with lansoprazole.

2.5.2 Age: The treatment of non-erosive GERD and EE in pediatric patients between 12 and 17 years old is the focus of this review. The mean age of all patients was 14.1 years.

Lansoprazole is approved for the treatment of non-erosive GERD and EE in adults and in pediatric patients between 1 and 11 years old.

2.5.3 Race: No safety or efficacy evaluation of racial subgroups was conducted in this pediatric population because the overwhelming majority (80.0%) of the adolescent patients was Caucasian.

2.5.4 Hepatic and Renal Impairment: Patients with severe renal or hepatic impairment were excluded from participating in the two studies; therefore, no comment can be made regarding pediatric patients with these conditions. Given similar PK of lansoprazole in pediatric patients between 12 and 17 years old and healthy adults, the adult recommendations should be applicable to this age group. The current lansoprazole label recommends no dosage adjustment for adult patients with renal insufficiency and dose adjustment should be considered for adults with severe hepatic disease.

2.5.5 Pregnancy: No patient was or became pregnant during the two studies. According to the current label, lansoprazole is considered Pregnancy Category B for adult patients.

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/s/

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Suresh Doddapaneni
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