Clinical Pharmacology and Biopharmaceutics Review

NDA: **20-406 / SE5-057**
21-281 / SE8-014
21-428 / SE8-004

Generic Name: Prevacid® Delayed-Release Capsule

Sponsor: Tap Pharmaceutical Products Inc.

Reviewer: Suliman I. Al-Fayoumi, Ph.D.

Type of Submission: Efficacy Supplement for Pediatric Labeling

Proposed Indication: Short term treatment of symptomatic GERD (non-erosive GERD and erosive esophagitis)

Submission Date: 12/23/03

ORM Division: GI & Coagulation Drug Products

OCPB Division: DPE II

Team Leader: Suresh Doddapaneni, Ph.D.

Proposed Dosage Regimen: 15 QD for up to 8 weeks for treatment of non-erosive GERD
30 mg QD for up to 8 weeks for treatment of erosive esophagitis

I. Executive Summary

Lansoprazole (Prevacid® Delayed-Release Capsule), a proton pump inhibitor, was approved for marketing in the US on 5/10/95. It is currently indicated for the treatment and maintenance therapy of a variety of acid-related GI conditions. The recommended adult dosage is 15-30 mg QD for up to 8 weeks.

To obtain needed pediatric information on lansoprazole, the Agency issued a formal Pediatric Written Request (PWR) for Prevacid® (lansoprazole) Delayed-Release Capsules on 8/26/98. The Agency requested in the PWR that the sponsor conduct single and multiple dose pharmacokinetic/pharmacodynamic (PK/PD) studies along with clinical outcome and safety evaluation in pediatric patients aged 0-12 months. In addition, the sponsor was to conduct studies to evaluate PK/PD and clinical outcomes in pediatric patients aged 1-11 years and 12-17 years corresponding to studies 3 and 4, respectively, of the PWR for Prevacid®

Based on submitted PK/PD and clinical safety and efficacy data, the sponsor recently gained approval for the use of Prevacid® in pediatric patients 1-11 years of age (see approval letter for NDA 20-406/SE5-047, dated 7/31/02).

The current submission is provided in support of the use of lansoprazole in pediatric GERD patients aged 12-17 years. The submission consists of two studies; study **M97-640** (a PK/PD study in adolescent GERD patients) and study **M00-158** (an 8-12 week open label safety and efficacy study).

The findings of study M97-640 indicate that Administration of 15 and 30 mg QD doses of lansoprazole results in similar values of the mean PK parameters (AUC and C_{max}) for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects. In addition, statistically significant increases in the values of the mean PD parameters (24-hr mean intragastric pH, % time pH > 3 & 4) are observed following 5 days of dosing relative to day 1.

The submitted studies are provided in partial fulfillment of the Agency's PWR for lansoprazole. Additional studies are currently being conducted by the sponsor in fulfillment of the remainder of the PWR.

A. Recommendations

From the view point of Office of Clinical Pharmacology and Biopharmaceutics, NDA 21-406 / S-057 is **acceptable** provided that a satisfactory agreement is reached between the Agency and the sponsor with respect to proposed language in the package insert. See Appendix 1 for the Agency proposed package insert.

The sponsor has adequately fulfilled the requirement for a study in pediatric GERD patients aged 12-17 years corresponding to study 3 in the Pediatric Written Request (PWR) for Prevacid®.

B. Phase IV Commitments

None.

II. Table of Contents

C. Summary of CPB Findings

NDA 20-406/S-057 consists of two studies; study **M00-158** (an 8-12 week open label safety and efficacy study), and study **M97-640** (a PK/PD study in adolescent GERD patients).

The current review solely addresses the Clinical Pharmacology and Biopharmaceutics-related results in the submission (i.e., study M97-640 which corresponds to study 3 of the PWR).

In study M97-640, the PK and PD profiles of lansoprazole in pediatric GERD patients aged 12-17 years were evaluated following administration of 15 or 30 mg capsules of Prevacid for a period of 5 days.

Administration of 15 and 30 mg doses of Prevacid resulted in similar mean AUC and C_{max} values for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects. When compared on PD data (mean 24-hr intragastric pH and % time pH > 3, 4, 5 & 6), the higher lansoprazole dose (30 mg) resulted in similar changes in the PD parameters relative to the lower dose (15 mg). In addition, statistically significant increases in mean 24-hr intragastric pH and % time pH > 3 & 4 were observed on day 5 relative to day 1.

II. Question-Based Review

A. General Attributes

Lansoprazole is a substituted benzimidazole that inhibits gastric acid secretion via specific inhibition of H^+/K^+ ATPase enzyme system at the secretory surface of the gastric parietal cell.

Lansoprazole is currently approved for use in adults and pediatric patients aged 1 to 11 years. The approved indications for adults in the U.S. include the short-term treatment of symptomatic gastroesophageal reflux disease (GERD) (15 mg once daily up to 8 weeks), the short-term treatment of erosive esophagitis (30 mg QD up to 8 weeks) and the long-term maintenance treatment of healed erosive esophagitis.

B. General Clinical Pharmacology

1. Are pediatric GERD patients aged 12-17 years and adults comparable on their PK/PD profiles?

Study M97-640 evaluated the PK and PD aspects of lansoprazole Capsule 15 and 30 mg in pediatric GERD patients aged 12-17 years. Sixty male and female pediatric GERD patients aged 12-17 years received 15 or 30 mg QD doses of Prevacid Delayed-Release Capsules for 5 consecutive days. The study was conducted in a randomized, open label, double-blind multi-center fashion. Blood samples were drawn for determination of lansoprazole PK up to 12 hrs post-dose on day 5, while 24-hr intragastric pH monitoring was conducted on days 1 and 5 of each treatment group.

Table 1. Summary of the mean PK parameters for Lansoprazole, 15 mg and 30 mg QD on day 5 (n = 59)

Pharmacokinetic Parameter (unit)	N	Lansoprazole 15 mg QD	N	Lansoprazole 30 mg QD	N	Healthy Adult Subjects[a]
T_{max} (h)	30	1.6 ± 0.7	29	1.7 ± 0.7	345	1.7 ± 0.8
C_{max}[b] (ng/mL)	30	414.8 ± 215.5	29	1005 ± 604.9	515	824 ± 419
Dose-normalized C_{max} (ng/mL/mg)	30	27.7 ± 14.4	29	33.5 ± 20.2	515	27.5 ± 14.0
AUC[b] (ng•h/mL)	30	1017 ± 1737	29	2490 ± 2522	513	2133 ± 1797
Dose-normalized AUC (ng•h/mL/mg)	30	67.8 ± 115.8	29	83.0 ± 84.1	513	71.1 ± 59.9
$t_{1/2}$[c] (h)	30	0.84 ± 0.26	29	0.95 ± 0.31	285	1.19 ± 0.52

SD = Standard Deviation

a Data obtained from Abbott-65006 Drug Metabolism Report No. 32 – Overview and summary of the human pharmacokinetics and biopharmaceutics of lansoprazole[10].

b For healthy adult subjects normalized to a 30 mg dose.

c Harmonic mean ± pseudo-standard deviation.

Table 1. Summary of the primary PD parameters for lansoprazole in pediatric GERD patients aged 12-17 years and healthy adult subjects.

Lansoprazole Dose	Day	Mean 24-hour Intragastric pH	% of time pH >3	% of time pH >4
Adolescents with GERD (M97-640)				
15 mg QD (N=10)	Baseline	2.7	27	20
	Day 5	3.8	59	47
30 mg QD (N=9)	Baseline	2.8	29	20
	Day 5	3.9	60	49
Adults Aged ≥18 years				
15 mg QD[a]	Baseline	2.1	18	12
	Day 5	4.0	59	49
30 mg QD[a]	Baseline	2.1	18	12
	Day 5	4.9	72	66

Administration of 15 and 30 mg doses of lansoprazole resulted in similar values of the mean PK parameters (AUC and C_{max}) for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects (Table 1).

When compared on PD data (mean 24-hr intragastric pH and % time pH > 3, 4, 5 & 6), both 15 mg and 30 mg doses resulted in similar changes in the PD parameters (Table 2). In addition, the PD data following administration of the 15 mg QD dose of lansoprazole seemed to be comparable between adolescent GERD patients and adults. As for the 30 mg dose of lansoprazole, values of the primary PD parameters appeared to be higher in adults relative to adolescent GERD patients.

Overall, the PK/PD data for Prevacid Delayed-Release Capsule in pediatric GERD patients aged 12-17 years indicate that the 15 mg and 30 mg QD doses of Prevacid are similar on their acid inhibitory effects in this age group. Based on the fact that PK was similar in adolescents and adults and 15 mg QD and 30 QD doses were found to be safe, in the safety and efficacy study M00-158, adolescent patients were dosed with 15 mg QD or 30 mg QD based on whether they had non-erosive GERD or erosive esophagitis (similar to adult dosing), respectively. In an uncontrolled, open-label, U.S. multicenter clinical study (study M00-158) involving 87 adolescent patients (12 to 17 years of age) with symptomatic GERD, both the 15 and 30 mg QD regimens were shown to be efficacious up to 8 to 12 weeks of treatment.

E. General Biopharmaceutics

None

F. Analytical Section

Plasma concentrations of lansoprazole were determined using a validated LC/MS/MS assay method over a range of 5 to 1200 ng/mL. The lower limit of quantitation was established at (b) (4).

III. Appendices

A. Proposed Package Insert (original and Agency proposed)

B. Individual Study Review

C. Cover Sheet and OCPB Filing/Review Form

Appendix A

Proposed Package Insert

34 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Appendix B

Individual Study Reviews

NDA: **20-406/ S-057 - Study M97-640** **Study Date**: **Mar 1998-Feb 1999**

Type of Study: **PK/PD Study in Adolescent GERD Patients**

Study **M97-640** is entitled,

"A Study to Evaluate the Effects of Lansoprazole 15 mg and 30 mg in Pediatric Patients with Esophagitis"

Primary Objective(s)

- To assess the safety, PK & PD of QD administration of lansoprazole in pediatric patients aged 12 to 17 with symptomatic GERD.

Study Design

Open-label, randomized, double-blind multi-center study

Subjects	60 pediatric patients
Key Inclusion Criteria	Male and female pediatric patients aged 12-17 yrs Had symptomatic, endoscopically and/or histologically proven GERD
Treatment	Patients were randomly assigned to receive one of two treatments: lansoprazole 15 mg OR lansoprazole 30 mg for a 5-day period.
PK/PD Sampling Times	For determination of lansoprazole plasma concentrations on day 5, blood samples were collected at the following time points: 0 (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10 and 12 hrs post-dose. For assessment of esophageal & gastric pH, a dual channel pH probe was placed nasogastrically and 24-hr pH measurements were continuously determined at baseline and during day 5 on treatment.

Pharmacokinetic/Pharmacodynamic Analysis

The following PK parameters were determined: AUC_{0-24}, C_{max}, t_{max}, $t_{1/2}$, CL/f & V_d/f. In addition, the following PD parameters were determined: mean 24-hr intragastric pH & % time pH > 3, 4, 5 & 6.

Results and Discussion

Table 1. Summary of the mean PK parameters for Lansoprazole, 15 mg and 30 mg QD on day 5 (n = 59)

Pharmacokinetic Parameter (unit)	N	Lansoprazole 15 mg QD	N	Lansoprazole 30 mg QD	N	Healthy Adult Subjects[a]
T_{max} (h)	30	1.6 ± 0.7	29	1.7 ± 0.7	345	1.7 ± 0.8
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b For healthy adult subjects normalized to a 30 mg dose.

c Harmonic mean ± pseudo-standard deviation.

Table 2. Summary of the mean PD parameters for Lansoprazole, 15 and 30 mg QD on day 5 and at baseline (n = 59)

	15 mg QD Lansoprazole (Mean ± SD)	
Variable Analyzed	**Baseline (N=10)**	**Day 5 Visit (N=10)**
24-hour Intragastric pH	2.71 ± 1.37	3.84 ± 1.34*
% of time pH >3	26.72 ± 28.40	58.92 ± 28.95*
% of time pH >4	19.99 ± 28.88	46.92 ± 30.92*
% of time pH >5	15.15 ± 29.42	31.97 ± 33.25
% of time pH >6	9.80 ± 24.61	13.96 ± 20.10
	30 mg QD Lansoprazole (Mean ± SD)	
Variable Analyzed	**Baseline (N=9)**	**Day 5 Visit (N=9)**
24-hour Intragastric pH	2.81 ± 1.56	3.89 ± 1.27*
% of time pH >3	29.11 ± 29.92	59.62 ± 27.61*
% of time pH >4	20.41 ± 30.64	48.91 ± 31.12*
% of time pH >5	15.08 ± 32.13	35.32 ± 32.36*
% of time pH >6	12.17 ± 31.51	13.96 ± 17.49

SD = Standard Deviation

* Statistically significantly different from the corresponding Baseline value ($p \leq 0.05$).

- Administration of 15 and 30 mg doses of lansoprazole resulted in similar mean PK parameters (AUC and C_{max}) for the pediatric GERD patients aged 12-17 years relative to healthy adult subjects (Table 1). In addition, AUC and C_{max} increased in a linear manner with dose from 15 mg to 30 mg. However, when compared on PD data (mean 24-hr intragastric pH and % time pH > 3, 4, 5 & 6), the higher lansoprazole dose (30 mg) resulted in similar changes in the PD parameters relative to the lower dose (15 mg) (Table 2).

- High inter-individual variability was observed with the mean PK parameter estimates (Table 1).
- Most of the measured PD parameters (mean 24-hr intragastric pH and % time pH > 3 & 4) on day 5 were statistically significantly increased when compared to baseline.
- The PD parameters for Lansoprazole in 12-17 year old pediatric GERD patients suggest that the 15 mg and 30 mg doses are similar on their acid inhibitory effects in this age group.

Appendix C

Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**20-406/SE5-057**	**Proposed Brand Name**	**Prevacid**
OCPB Division (I, II, III)	**II**	**Generic Name**	**Lansoprazole**
Medical Division	**GI & Coagulation**	**Drug Class**	**Proton Pump Inhibitor**
OCPB Reviewer	**Suliman Al-Fayoumi**	**Indication(s)**	**Acid-related conditions**
OCPB Team Leader	**Suresh Doddapaneni**	**Dosage Form**	**Delayed Release Capsule**
		Dosing Regimen	**15/30 mg QD**
Date of Submission	**12/23/03**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**5/23/04**	**Sponsor**	**Tap Pharmaceutical Products, Inc.**
PDUFA Due Date	**6/22/04**	**Priority Classification**	**Priority**
Estimated Division Due Date	**5/30/04**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	**1**	**1**	**1**	

Phase 3 clinical trial:				
Population Analyses –				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies	**1**	**1**	**1**	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	**X**	
Comments sent to firm ?	**Not needed at this time**	
QBR questions (key issues to be considered)	**1. Are pediatric GERD patients aged 12-17 years and adults comparable on their PK/PD profiles?**	
Other comments or information not included above		
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

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

/s/

Suliman Alfayoumi
6/7/04 12:24:59 PM
BIOPHARMACEUTICS

Suresh Doddapaneni
6/7/04 12:41:35 PM
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