CLINICAL PHARMACOLOGY REVIEW

NDA: 20,973 / S-022	Submission Date: 12/31/07, 04/07/08, 05/09/08, 6/10/08, 6/11/08
Submission Type; Code:	Pediatric Supplement
Brand Name:	Aciphex
Generic Name:	rabeprazole
Primary Reviewer:	David Gortler
Team Leader	Sue-Chih Lee
OCP Division:	3
OND Division:	Division of Gastroenterology Products
Sponsor:	Eisai Medical Research
Formulation; Strength(s):	Delayed-Release Tablets, [redacted] 20mg
Proposed Indication:	[redacted] gastroesophageal reflux disease (GERD).
Proposed Dosage and Regimen:	[redacted] 20mg qd

Table of Contents

1 Executive Summary

1.1 Recommendations

The application is acceptable from a clinical pharmacology perspective provided that a mutual agreement regarding the label language can be reached between the sponsor and Agency.

Protocol #E3810-A00-119 fulfills part of the phase IV commitment. Specifically, it has addressed the pharmacokinetic component for pediatric patients aged 12-16 years. In addition, from a clinical pharmacology perspective, the design of this study is consistent with that for Study 5 in the Pediatric Written Request dated July 10, 2007. The comment below should be communicated to the Medical officer of HFD-180.

1.2 Comment

Based on the PK data provided, the dosing regimen of 20 mg QD (b) (4) is appropriate for adolescent patients aged 12-16 years in terms of efficacy.

1.3 Phase IV Commitments

At the time of the NDA approval in 1999, the sponsor committed to conduct a study to assess the optimal dosage regimen in the pediatric population for the healing and maintenance of healing of GERD. In the Pediatric Written Request issued in 2007, the sponsor was requested to conduct five studies in pediatric patients covering the age groups of neonates and pre-term infants (of <44 weeks of age) up to adolescents of 16 years. As the current NDA addresses the age group of 12-16 years, (b) (4)

1.4 Summary of Clinical Pharmacology and Biopharmaceutics Findings:

Background:

Aciphex was first approved in 8/1999 for the treatment of erosive and symptomatic GERD in adults with the stipulation that there would be further Phase 4 studies done in the pediatric population. The currently approved adult dose is 20mg QD.

In the current submission, the sponsor is pursuing the pediatric indication for rabeprazole in the short-term treatment of GERD in adolescent patients 12 to 16 years of age. The proposed dose (b) (4) 20mg QD.

To support this NDA, the sponsor submitted two clinical studies. Protocol E3810-A00-119 was a single and multiple dose pharmacokinetics and safety study in pediatric patients aged 12-16 years. Protocol # E3810-A001-202 was a safety and efficacy study of rabeprazole in the Treatment of GERD in 12-16 year old subjects. This latter study is being reviewed by Dr. Wen-Yi Gao, Medical Officer of DGP.

Review of Protocol E3810-A00-119

In this open-label, single- and multiple-dose study patients were stratified by age (12 to 14 and 14 to 16 years of age) and assigned to one of the two doses (10 mg and 20 mg; 12 subjects per dose group) for a total of 24 subjects. This drug was given following an overnight fast on Days 1, 2 and 5 (or 7).

20-mg dose group:
Following oral administration of Aciphex 20 mg once daily, peak plasma concentrations occurred at approximately 4 hours postdose. Mean (±SD) PK parameters on Day 1 and Day 5/7 for the 20 mg dose are shown in Table 1. Again, high inter-subject variability in PK parameters was observed with the %CV ranging from 52.5% to 64.5% for Cmax and ~65% for AUC. The terminal half-life was approximately 1.0 hour. Therefore, no accumulation was expected for once daily dosing.

On Day 5/7, mean Cmax and AUC were each approximately 40% higher than the Day 1 values, respectively. The reason for this observation is unknown. One likely explanation is the high intra-subject variability. Another possibility is that the pH in the GI tract might be higher after multiple dosing, resulting in greater bioavailability due to better stability of rabeprazole at higher pH. It is noted that the current label states that multiple dosing does not change PK in adults.

10-mg dose group:
The PK parameters following oral administration of Aciphex 10 mg once daily for 5 to 7 days in adolescent patients are presented in Table 1. No increase in exposure was observed on Day 5/7 compared to Day 1. The inter-subject variability in PK parameters ranged from approximately 30-50%.

Note: The sponsor did not plot the data points when the concentrations were below the quantifiable limit. As a result, some of the concentration-time profiles appeared to have incomplete data up to the 2-3 hour time point. As a general rule, the BLQ data points should be presented in plots.

TABLE 1:

Comparison of Mean (SD*) PK Parameters on Day 1 and Day 5 or Day 7 in Subjects 12 to 16 years of Age (E3810-A001-119)

Study Day/PK Parameters	E3810 10 mg		E3810 20 mg	
	N	Mean (SD)	N	Mean (SD)
Day 1				
$AUC_{0\text{-}inf}$ (ng*hr/mL)	8	305.0 (107.2)	11	557.8 (364.3)
C_{max} (ng/mL)	12	186.6 (88.21)	12	319.0 (167.59)
T_{max} (hr)	12	3.3 (1.12)	12	3.9 (0.69)
$T_{1/2}$ (hr)	8	0.545 (0.120)	10	1.037 (0.856)
CL/F/Wt(mL/min/kg)		NC		NC
Day 5 or 7				
$AUC_{0\text{-}inf}$ (ng*hr/mL)	9	249.8 (95.2)	9	828.4 (528.3)
C_{max} (ng/mL)	11	184.1 (88.17)	12	460.4 (297.31)
T_{max} (hr)	11	3.4 (1.72)	12	4.1 (1.55)
$T_{1/2}$ (hr)	8	0.575 (0.178)	8	0.974 (0.530)
CL/F/Wt(mL/min/kg)	9	12.58 (5.479)	9	10.14 (6.907)

*SD = standard deviation
NC = not calculated

PK Parameters: Pediatric Patients vs. Adults :

Variability in PK parameters was high in both adult and pediatric subjects. Both AUC and Cmax for the 20mg dose in adolescents were within the ranges observed for the approved dose of 20 mg in studies in adults. The 10 mg dose in adolescent patients resulted in substantially lower exposure compared to the approved dose (20 mg) in adults.

Dosing regimen for pediatric patients aged 12-16 years:
The disease (GERD) and drug response, including the concentration-response, are considered to be similar between adults and adolescents. Therefore, PK data can be used as a surrogate for efficacy.

The dosing regimens proposed by the sponsor are [redacted] 20 mg QD. Following 10 mg QD dosing in adolescents patients, both Cmax and AUC were substantially lower than those found for the approved 20 mg QD dosing in adults. Therefore, the PK data provided do not support the efficacy of the 10 mg QD dosing regimen in adolescent patients and additional data will be necessary for this purpose.

Both AUC and Cmax for the 20mg QD dosing in adolescents were within the range observed in adult studies for 20 mg QD dosing. Therefore, we consider the dosing regimen of 20 mg QD appropriate for adolescent patients aged 12-16 years.

2 QBR

2.1 General Attributes of the Drug

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

The sponsor committed to conduct rabeprazole pediatric studies as a Phase 4 commitment in conjunction with the approval in 1999 of rabeprazole sodium delayed-release tablets for the treatment of erosive and symptomatic GERD in adults. Based on the Pediatric Written Request (PWR) for Aciphex, Amendment #5, July 10, 2007 to support the use of rabeprazole sodium in short-term treatment of GERD in adolescents 12 to 16 years of age, the studies below were requested by the FDA.

Therefore, the submitted pediatric study was evaluated in relation to both the phase 4 commitment and the PWR. It was concluded that Study E3810-A00-119 fulfills part of the phase 4 commitment and its study design was consistent with Study 5 Part (a) as delineated in the PWR.

> a) Study 5 Part (a): To characterize the pharmacokinetic (PK) profile of single and repeated doses of rabeprazole in subjects 12 to 16 years of age. At least 12 subjects in at least 2 dose levels (ie, at least 6 per treatment group) were required to complete the study. N=24

Study E3810-A00-119, titled "Single and Multiple Dose Pharmacokinetics and Safety Study of Rabeprazole Sodium in l2 to l6 Year Old Subjects", was conducted to fulfill this requirement.

b) Study 5 Part (b): To collect information on the safety of single and repeated doses of rabeprazole in pediatric subjects 12 to 16 years of age. N=107

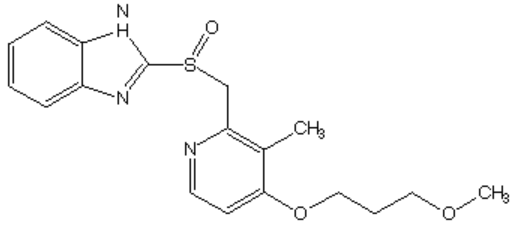
Study E3810-A001-202, titled: "Safety and Efficacy of Rabeprazole in the Treatment of GERD in 12-16 Year Old Subjects" was conducted to fulfill this requirement.

(b) (4)

2.1.2 Highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product.

Drug Product:
The tablets are enteric coated (to prevent denaturing by the gastric acid) and delayed-release, enteric coated tablet should be swallowed whole and not chewed, crushed, or split.

Drug Substance: Rabeprazole



Chemical Formula: C18-H21-N3-O3-S with a molecular weight of 381.43

2.1.3 What are the proposed mechanism of action and therapeutic indication(s)?

Rabeprazole sodium, also known in the scientific literature as E3810, is a substituted benzimidazole molecule that is an inhibitor of H^+, K^+ adenosine triphosphatase (ATPase), the proton pump responsible for the terminal step in gastric acid secretion. It has been shown, in various in vivo and in vitro models, to be an anti secretory agent with dose-dependent activity. Rabeprazole is extensively metabolized by the liver to a thioether and sulphone metabolite. These metabolites are formed by the cytochrome P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole) system. However, neither metabolites have significant antisecretory activity.

Adult FDA approved indications:

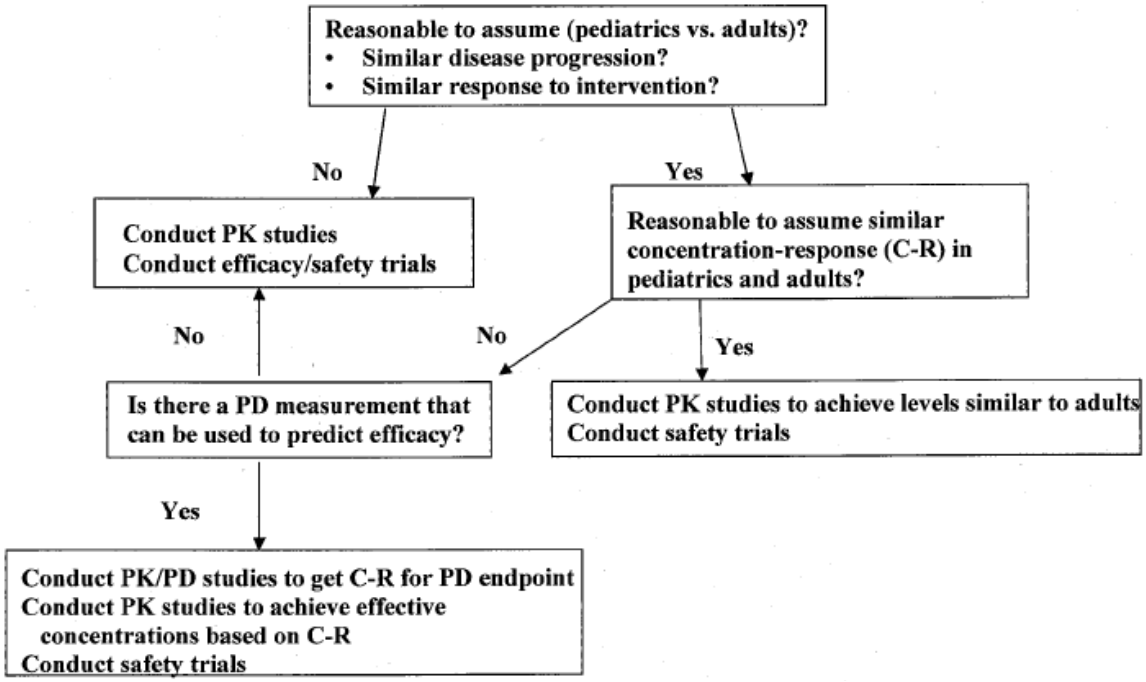
- Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) 20 mg once daily
- Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD) 20 mg once daily
- Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD) 20 mg once daily
- Healing of Duodenal Ulcers: 20 mg once daily
- Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence Three Drug Regimen: (ACIPHEX 20 mg, Amoxicilin 1000 mg, and Clarithromycin 500 mg) Twice Daily for 7 days
- Treatment of Pathological Hypersecretory Conditions, Including Zollnger-Ellson Syndrome Staring dose 60 mg once daily

Proposed pediatric indication:
The indication as proposed by the sponsor is the treatment of Gastroesophageal Reflux Disease (GERD).

2.1.4 Are the disease and pharmacological response to rabeprazole similar between adults and adolescents?

Older children and adolescents also experience GERD, and in these age groups GERD is more like the disease in adults in its pathophysiology and presentation. The pharmacological response in adolescents is also expected to be similar to that in adults.

The symptoms of GERD in older children and adolescents, which is the age group examined in the current study include retrosternal or epigastric pain, regurgitation, vomiting, and dysphagia also occur in adults. Therefore, in patients aged 12-16 years, PK data can be used as a surrogate for efficacy and no additional clinical efficacy data are required.



2.1.5 What are the proposed dosing regimens and route of administration?

(b) (4) 20mg orally, once daily

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the pivotal PK studies?

This was an open-label, single- and multiple-dose study characterizing the PK profile and evaluating the safety of rabeprazole sodium in subjects 12 to 16 year of age. Subjects at 7 study centers who had a diagnosis of, or symptoms of GERD were stratified by age (12 to < 14 and 14 to 16 years of age) and assigned to one of the two dose groups (12 subjects per dose group, approximately six subjects per age stratum) for a total of 24 subjects. Subjects participated in only one dose group (10 or 20 mg). A total of 24 subjects at seven investigational sites completed their participation in the study.

Doses based on two tablet strengths (10 and 20 mg rabeprazole sodium) were administered to the subjects in an ascending dose fashion, beginning with 10 mg. Administration of the 10 mg dose was completed and preliminary safety data was evaluated before administration of the 20 mg dose was initiated. Each subject

participated for a total of up to three weeks, including the screening visit, which was scheduled within two weeks of study drug administration.

Blood samples for pharmacokinetic analysis will be obtained on Days 1 and 5 (or 7) at predose, 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours after dosing.

2.2.2 What are the PK parameters in the pediatric population aged 12-16 years?

The mean rabeprazole plasma concentration-time profiles following oral administration of rabeprazole 10 mg or 20 mg for 5 to 7 days are presented in Figures 1 and 2 for Day 1 and Day 5/7 data, respectively.

10-mg dose group:
Following oral administration of Aciphex 10 mg group subjects had little change in AUC, when comparing Day 1 with Day5/7 values. Some of the graphs appeared to have incomplete data up to the 2-3 hour time point until it was made clear on 6/10/08 by the sponsor that the BLQ data was not plotted. For completeness, the BLQ points should be plotted.

20-mg dose group:
Following oral administration of Aciphex 20 mg, peak plasma concentrations occurred at approximately 4 hours postdose. Mean (±SD) PK parameters on Day 1 and Day 5/7 for the 20 mg dose are shown in Table 1. High inter-subject variability in PK parameters was observed with the %CV ranging from 52.5% to 64.5% for Cmax and ~65% for AUC. The terminal half-life was approximately 1.0 hour. Therefore, no accumulation was expected for once daily dosing.

On Day 5/7, mean Cmax and AUC were approximately 40% higher when compared to Day 1 values (Figure 4). The exact reason for this observation is unknown. However, one distinct possibility is that the pH in the GI tract might be higher after multiple dosing, resulting in higher bioavailability due to better stability of rabeprazole at higher pH.

It is noted that the current label states that multiple dosing does not change PK in adults. Overall, this increase in exposure following multiple dosing was not consistently observed across studies and high intra-subject variability in PK might play a role in these inconsistent findings.

Concentrations of rabeprazole over time illustrating differences on Day 1 versus Day 5 or 7, for 10 versus 20mg doses.

FIGURE 1

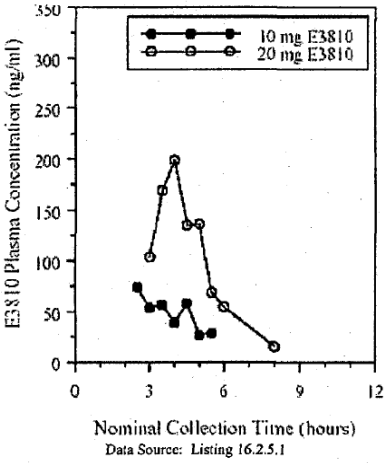


Figure 1: E3810 plasma concentrations on Day 1

FIGURE 2

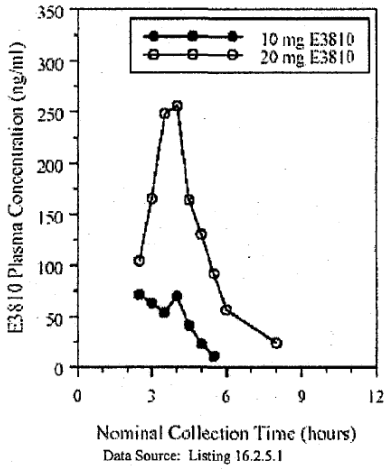


Figure 2: E3810 plasma concentrations on Day 5 or 7

Mean plasma concentrations graphs of rabeprazole over time for A) 10 and B) 20mg doses, respectively showing an increased AUC on Day 1 versus Day 5 or 7.

FIGURE 3

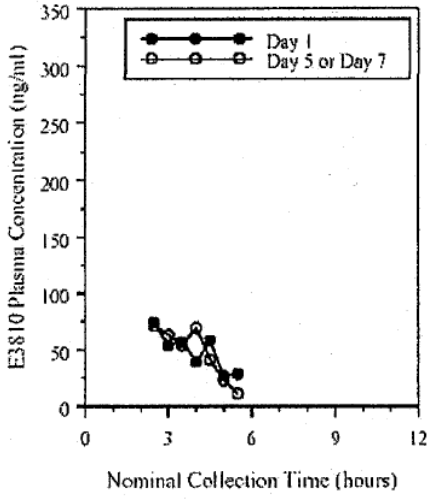
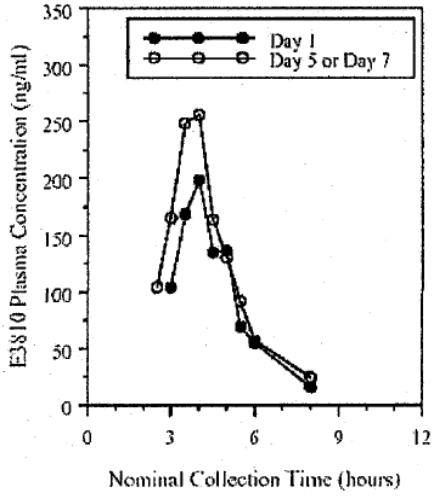


FIGURE 4



Figures 1-4: Some of the graphs appeared to have incomplete data up to the 2-3 hour time point until it was made clear by Eisai that for an unknown reason, BLQ data was not plotted. It is preferred the BLQ points be plotted.

Comparison of Mean (SD*) PK Parameters on Day 1 and Day 5 or Day 7 in Subjects 12 to 16 years of Age (E3810-A001-119)

Study Day/PK Parameters	E3810 10 mg		E3810 20 mg	
	N	Mean (SD)	N	Mean (SD)
Day 1				
$AUC_{0\text{-}inf}$ (ng*hr/mL)	8	305.0 (107.2)	11	557.8 (364.3)
C_{max} (ng/mL)	12	186.6 (88.21)	12	319.0 (167.59)
T_{max} (hr)	12	3.3 (1.12)	12	3.9 (0.69)
$T_{1/2}$ (hr)	8	0.545 (0.120)	10	1.037 (0.856)
CL/F/Wt(mL/min/kg)		NC		NC
Day 5 or 7				
$AUC_{0\text{-}inf}$ (ng*hr/mL)	9	249.8 (95.2)	9	828.4 (528.3)
C_{max} (ng/mL)	11	184.1 (88.17)	12	460.4 (297.31)
T_{max} (hr)	11	3.4 (1.72)	12	4.1 (1.55)
$T_{1/2}$ (hr)	8	0.575 (0.178)	8	0.974 (0.530)
CL/F/Wt(mL/min/kg)	9	12.58 (5.479)	9	10.14 (6.907)

*SD = standard deviation
NC = not calculated

2.2.3 Are the proposed dosing regimens [redacted] 20 mg QD) appropriate?

The 20 mg QD dosing regimen is appropriate for adolescents patients aged 12-16 years. [redacted]

PK for Pediatric vs. Adult:
A comparison between existing adult data and the data from this trial was made in order to compare the PK parameters between the two populations and assess for similarity. Rabeprazole, has been extensively studied in adults. The current study represents the first investigation of rabeprazole in adolescents 12 to 16 years of age. Adult PK data from the following studies are used for comparison with the pediatric data:

- E3810-A001-001 was a randomized, double-blind, placebo-controlled, sequential group, single dose escalating study in healthy male subjects. (n=8)

- E3810-A001-002 was a double-blind, randomized, placebo-controlled sequential-group, multiple dose escalating study in healthy male subjects following 14 consecutive days single, daily, oral dose administration. (n=6)

- E3810-A001-009 was a randomized, open-label, 4-period, 2-sequence crossover 20 mg single dose bioequivalent study in healthy male and female subjects. (n=88)

10-mg dose:
Following 10 mg QD dosing in adolescents patients, both Cmax and AUC were substantially lower than those found for the approved 20 mg QD dosing in adults. Therefore, the PK data provided do not support the efficacy of the 10 mg QD dosing regimen in adolescent patients and additional data will be necessary to demonstrate its efficacy.

20-mg dose:
Upon our request, the sponsor provided the table and scatter plots as shown below. Inter-subject variability for PK parameters was high in both adult and pediatric studies. The plots revealed that both AUC and Cmax for the 20mg QD dosing in adolescents were within the range observed in adult studies for 20 mg QD dosing. Therefore, we consider the dosing regimen of 20 mg QD appropriate for adolescent patients aged 12-16 years.

Summary of Mean PK Parameters of Rabeprazole on Day 5 or Day 7 in 12 to 16 Year Old Subjects Compared with Healthy Adults in Previous Studies following 20 mg QD dosing

PK Parameter	Rabeprazole 20 mg	
	Adolescents Mean ± SD (range) (n=)	**Adults** Mean ± SD (study number) (n=)
AUC0-t (ng*hr/mL)	731±501 (137-1864) (n=12)	545 ± 215 (001)b (n=8)
		435 ± 260 (002)a (n=6)
		828±378 (009)c (n=88)
Cmax (ng/mL)	460±297 (88.6-999) (n= 12)	294 ± 101 (001) (n=8)
		253 ± 184 (002)a (n=6)
		594 ± 269 (009) (n=88)
Tmax (hr)	4.1±1.56 (2.5-8.0) (n=12)	2.9 ± 0.35 (001) (n=8)
		2.7 ± 1.7 (002)a (n=6)
		3.6 ± 0.80 (009) (n=88)
T1/2 (hr)	0.974±0.529 (0.380-1.88) (n=8)	0.70 ± 0.16 (001) (n=7)
		1.2 ± 0.39 (002)a (n=6)
		1.2 ± 0.77 (009) (n=88)
Cl/F/Wt (mL/min/kg)	10.1±6.91 (1.81-24.2) (n=9)	9.56 ± 5.86 (001) (n=8)
		15.4 ± 11.2 (002)a (n=6)
		NC (009)

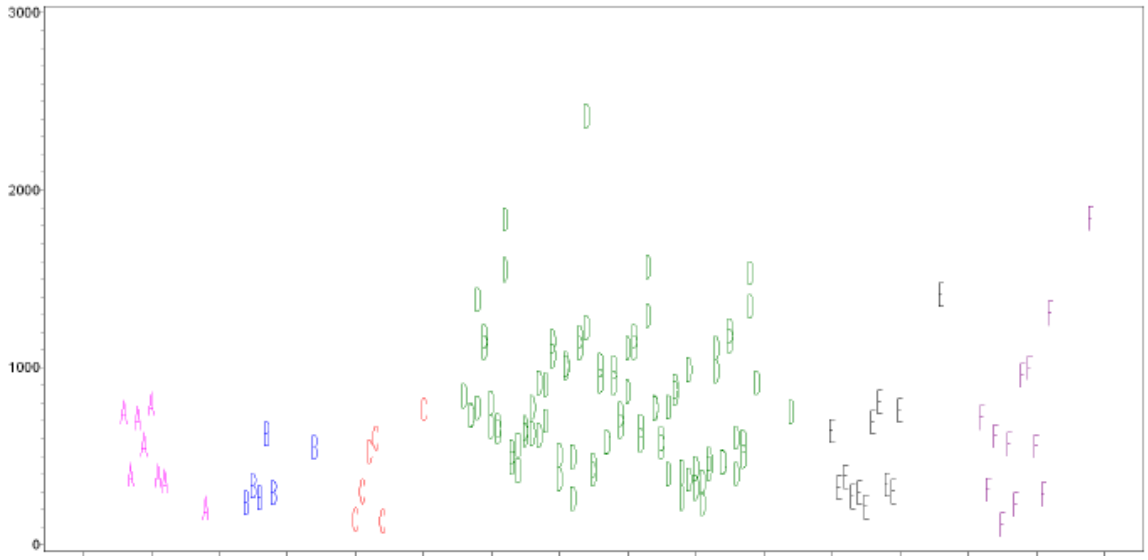
NC = Not calculated: n is the number of observations
[a] PK parameters from Day 5 of multiple-dose study. All other adult PK parameters are from single-dose studies.
[b]: AUC was calculated from hour 0 to hour 24
[c] Table 3 in section 2.7.2 erroneously reported $AUC_{0\text{-inf}}$ This updated table includes the corrected value, $AUC_{0\text{-t}}$

A E3810-A001-001 (Day 1)
B E3810-A001-002 (Day 1)
C E3810-A001-002 (Day 5)
D E3810-A001-009 (Day 1)
E E3810-A001-119 (Day 1)
F E3810-A001-119 (Day 5 or 7)

Scatter plot for individual Cmax (ng/mL) Rabeprazole 20mg

(b) (4)

Scatter plot for individual AUC0-last(ng*h/mL) Rabeprazole 20mg



Note: Some of the more significant outliers with the highest AUC and Cmax values for adults on Day 1 in the 20mg studies shown graphically above may be poor 2C19 metabolizers.

2.2.2.1 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) for safety? If relevant, indicate the time to the onset and offset of the pharmacological response or clinical endpoint.

The following results were obtained from Dr. Wen-Yi Gao, Medical Officer of HFD-180.

No statistically significant differences were observed between the two dose groups for the number of subjects with individual AEs. Rabeprazole, administered as either a 10 mg or 20 mg dose to 12 to 16 year old subjects with GERD, was safe and well tolerated.

Almost all of the AEs reported were of mild intensity, and five subjects (20.8%) had AEs considered to be possibly related to study drug. Six subjects (25.0%) had TEAVS, three in each dose group; none of the TEAVs were considered by the investigator to be clinically significant. No clinically meaningful changes in the mean values in any of the vital signs during the study were noted in either treatment group. None of the normal findings at screening for physical examinations shifted to abnormal at the Day 6 or 8 Discharge Evaluations.

With the exception of one subject (4.2%) reporting an AE of moderate severity (dysmenorrhea), all AEs were of mild severity (41.7% of subjects). No severe AEs were reported. Overall, 5 subjects (20.8%) reported AEs that were considered to be related to study drug: 3 in the 10 mg and 2 in the 20 mg group. These five subjects had AEs that were considered to be possibly related; none were considered probably related to study drug. Treatment-related AEs consisted of the following in one subject each: diarrhea, headache, nausea, periorbital edema, and proteinuria.

2.2.3 How is this drug metabolized?

Rabeprazole is extensively metabolized to a thioether and sulphone metabolite, neither of which have significant activity. These metabolites are formed by the cytochrome P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole) system.

2.2.3.1 Is the drug a substrate of CYP enzymes?

Yes:

1. CYP 2C19, yielding desmethyl rabeprazole
2. CYP 3A, yielding a sulphone metabolite

Neither metabolite is pharmacologically active.

2.2.3.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

According to the package labeling, larger adult studies have not found rabeprazole to be an inducer of 2C19.

2.3 General Biopharmaceutics

2.3.1 What is the effect of food on the bioavailability (BA) of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

In the present study, rabeprazole was administered under fasting conditions. According to the package labeling, in adults, when rabeprazole was administered with food, a prolongation in time to peak plasma levels is evident (about 1.5 hours); however, peak plasma concentrations and AUC values remained essentially unaltered.

2.4 Analytical Section

2.4.1 How are the active moieties identified and measured in the plasma in the clinical pharmacology and biopharmaceutics studies?

Rabeprazole plasma concentrations (including the main metabolite of rabeprazole: rabeprazole thioether (rab-TH, PTBI)) were measured by a validated liquid chromatography/tandem mass spectrometry system (liquid chromatography/mass spectrometry/mass spectrometer (LC/MSIMSD (b) (4) The assay was validated in both sodium heparin plasma and EDTA plasma. The sample volume was 25 µL. The assay range for both E3810 and PTBI is 5 to 1000 ng/mL.

(b) (4)

Table 1. Validation Assay Performance Summary for E3810 and PTBI

Report Title	LC/MS/MS Assay Validation of E3810 and PTBI in Human Plasma
Report Number	(b) 45-0302
Analyte Names	E3810, PTBI
Internal Standard (IS)	(b) (4)
Analytical Method Type	LC/MS/MS
Extraction Method	Liquid/liquid
QC Concentrations	5, 15, 200 and 900 ng/mL
Standard Curve Concentrations	5, 10, 30, 100, 300, 600 and 1000 ng/mL
Lower Limit Of Quantitation (ng/mL)	5 ng/mL for E3810 & PTBI
Upper Limit Of Quantitation (ng/mL)	1000 ng/mL for E3810 & PTBI
Average Recovery of E3810 (%)	98.3%
Average Recovery of PTBI (%)	104.8%
Average Recovery of Int. Std (%)	(b) (4)
QC Intraday Precision Range (%CV) for E3810	3.9 to 8.8%
QC Intraday Precision Range (%CV) for PTBI	1.6 to 10.3%
QC Intraday Accuracy Range (%Diff) for E3810	-3.1 to 5.7%
QC Intraday Accuracy Range (%Diff) for PTBI	-9.8 to 3.3%
QC Interday Precision Range (%CV) for E3810	6.5 to 7.8%
QC Interday Precision Range (%CV) for PTBI	4.6 to 7.2%
QC Interday Accuracy Range (%Diff) for E3810	-0.3 to 7.9%
QC Interday Accuracy Range (%Diff) for PTBI	-1.5 to 1.4%

(b) (4)

Table1. Validation Assay Performance Summary for E3810 and PTBI	
Benchtop Stability of both compounds in NaOH treated human plasma	24 Hours
Freeze/thaw Stability of both compounds in NaOH treated human plasma	3 Cycles at -20°C and -70°C
Long-term Storage Stability in NaOH treated human plasma	373 Days at -20°C and -70°C[b]
Autosampler Stability in Reconstitution Solvent	193 hour at 4°C
Dilution integrity	1500 ng/mL diluted 10-fold
Selectivity	≤ 20% LLOQ for analyte (b) (4)

CV = coefficient of variation Diff = differential; (b) (4) LC/MS/MS = liquid chromatography tandem mass spectrometry; LLOQ = lower limit of quantification; NaOH = sodium hydroxide; QC = quality control; (b) (4)

[a] LC/MS/MS Assay Validation of E3810 and PTBI in Human Plasma, (b) (4) Validation Report (Addendum #1)

[b] LC/MS/MS Assay Validation of E3810 and PTBI in Human Plasma, (b) (4) Validation Report (Addendum #2)

Source: LC/MS/MS Assay Validation of E3810 and PTBI in Human Plasma, (b) (4)

3 Detailed Labeling Recommendations

Pediatric:

12 -16 Years of Age

The pharmacokinetics of rabeprazole was studied in 12 adolescent patients with GERD 12 to 16 years of age, in a multicenter study. Patients received rabeprazole 20 mg once daily for five to seven days. A 40% increase in exposure was noted following approximately one week of dosing. Pharmacokinetic parameters in adolescent patients with GERD 12 to 16 years of age were within the range observed in healthy adult volunteers.

17 Page(s) Withheld

_____ Trade Secret / Confidential

__X__ Draft Labeling

_____ Deliberative Process

4.2 Individual Study Review (study design and safety summary only)

Title:

Study E3810-A00-119: Single and Multiple Dose Pharmacokinetics and Safety Study of Rabeprazole Sodium in l2 to l6 Year Old Subjects.

Study Objective:

The primary objective of the study was to characterize the PK profile of single and repeated doses of rabeprazole sodium in subjects 12 to 16 years of age with a diagnosis of, or symptoms of, GERD. This study used the commercially available form of Aciphex already approved for use in adults.

Study design:

This was an open-label, single- and multiple-dose study characterizing the PK profile and evaluating the safety of rabeprazole sodium in subjects 12 to 16 year of age. Subjects were stratified by age (12 to 14 and 14 to 16 years of age) and assigned to one of the two doses (12 subjects per dose group, approximately six subjects per age stratum) for a total of 24 subjects. Subjects participated in only one dose group (10 or 20 mg). This was a single dose study with a 5/7 Day multiple-dose run-in. This drug was given following an overnight fast and without breakfast on Days 1, 2 and 5 (or 7). Subjects were allowed liquids 2 hours post dose and lunch 4 hours post dose. A total of 24 subjects at eight investigational sites completed their participation in the study.

Pharmacokinetic Sampling Scheme:

Blood samples for PK determinations were to be obtained during treatment on study Days 1, 2, 3, 4, and 5 (or 7) and at the discharge evaluation on Day 6 (or Day 8). Pharmacokinetic parameters included: Cmax, Tmax. t1/2, AUC_{0-t}. $AUC_{0-\infty}$ Rac, Cavss, CL/F, and Vz/F.

Blood samples for pharmacokinetic analysis will be obtained on Days 1 and 5 (or 7) at predose, 30 min, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 8, and 12 hours after dosing.

Pharmacokinetics:

Pharmacokinetic parameters for rabeprazole (parent compound) were calculated from the rabeprazole and PTBI plasma concentrations obtained from blood samples collected on Day 1 (predose and postdose), Days 2, 3, and 4 (all predose), and Days 5 (or 7) (predose and postdose) and Days 6 (or 8) (postdose).

Safety Summary:

No deaths or SAEs were reported, and no subjects were discontinued from the study due to AEs. The incidence of Treatment-Emergent Signs and Symptoms (TESS) was 45.8%, and headache was the most frequently reported TESS (4 subjects, 16.7%), followed by nausea (2 subjects, 8.3%). No statistically significant differences were observed between treatments for the number of subjects with individual AEs. Almost all of the AEs reported were of mild intensity, with 10 subjects (41.7%) having mild AEs and one subject (4.2%) having a moderate AE. Five subjects (20.8%) had AEs considered to be related to study drug. All of these AEs were considered to be possibly related to study drug.

None of the Treatment Emergent Abnormal (laboratory) Values (TEAVs) were considered by the investigator to be clinically significant. No clinically-meaningful-

changes in the mean values in any of the vital signs during the study were noted in either treatment group.

4.3 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	20-973/S-022	**Brand Name**	Aciphex
OCP Division (I, II, III)	DCP III	**Generic Name**	rabeprazole
Medical Division	Division of GI	**Drug Class**	PPI
OCP Reviewer	David Gortler	**Indication(s)**	GERD
OCP Team Leader	Sue-Chih Lee	**Dosage Form**	tablet
		Dosing Regimen	[redacted]20mg once daily for 12-16 year olds
Date of Submission	December 28th 2007	**Route of Administration**	oral
Estimated Due Date of OCP Review	--	**Sponsor**	Eisai
PDUFA Due Date	June 30th 2008	**Priority Classification**	priority
Division Due Date	May 20th 2008		

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	x	1	1	**DG reviews this**
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:	**x**	**1**	1	
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
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	**x**			
Literature References				
Total Number of Studies		2	2	

Filability and QBR comments		
	"X" if yes	Comments
Application filable ?	x	
Comments sent to firm ?		
QBR questions (key issues to be considered)	Does #119 fulfill the phase 4 commitment? Is study 119 designed consistently with the written request?	
Other comments or information not included above		
Primary reviewer Signature and Date	David Gortler, 6/18/2008	
Team Leader Signature and Date	Sue-Chih Lee, 6/18/2008	

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

/s/

David S Gortler
6/20/2008 03:14:56 PM
BIOPHARMACEUTICS

Sue Chih Lee
6/20/2008 03:40:35 PM
BIOPHARMACEUTICS