DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Joyce Korvick Deputy Director Division of Gastroenterology Products Office of New Drugs III Center for Drug Evaluation and Research
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	NDA 20-973
Applicant Name	Eisai Medical Research Inc.
Date of Submission	December 31, 2007
Proprietary Name / **Established (USAN) Name**	Aciphex (rabeprazole sodium)
Dosage Forms / Strength	Delayed Release Tablets 10 & 20 mg
Administration	Oral 1 q day
Proposed Indication(s)	Treatment of Symptomatic GERD in pediatric patients 12 years of age and above.
Action/Recommended Action:	**Approval of 20 mg dose only, with Patient Package Insert (not for safety). No PREA requirements or Post-marketing Requirements.**

1. Introduction

Aciphex (rabeprazole) is a member of the Proton Pump Inhibitor Class of drugs. Aciphex 20 mg was approved August 18, 1999. Subsequently, Aciphex 10 mg was approved on May 29, 2002 as a CMC supplement. However, Aciphex 10 mg was never marketed in the U.S due to considerations of off label dosing in the pediatric population. The current efficacy supplement provides for an addition of a new pediatric population (12 to 16 year olds) in partial response to Written Request (WR) and post marketing commitments under the Pediatric Research Equity Act (PREA).

Aciphex 20 mg is currently indicated for the following in adults:

- Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)
- Maintenance of Healing of Erosive or Ulcerative GERD
- Treatment of Symptomatic GERD
- Healing of Duodenal Ulcers
- Helicobacter pylori Eradication to Reduce the Risk of Duodenal Ulcer Recurrence
- Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

This supplement requests the addition of the following indication:

"1.3. Treatment of Symptomatic Gastroesophageal Reflux Disease (GERD)"

"ACIPHEX is indicated for the treatment of daytime and nighttime heartburn and other symptoms associated with GERD in adults and adolescents 12 years of age and above."

Dosage and Administration:
"2.7 Short-term Treatment of Gastroesophageal Reflux Disease (GERD) in Adolescent Patients 12 years of age and above"
"The recommended oral dose for adolescents 12 years of age and above is 20 mg once daily for up to 8 weeks."

2. Background

This submission is a partial response to the Pediatric Written Request for studies in pediatric patients for GERD (gastroesophageal reflux disease). It includes final reports of pre-clinical studies, and clinical studies E3810-A001-119 and E3810-A001-202. Study E3810-A001-119 is a pharmacokinetic study with 24 pediatric GERD patients 12 to 16 years old. Patients were exposed to two dose levels (10 mg or 20 mg) for 5 to 7 days. The extension of the indication of the treatment of Symptomatic GERD is based upon the similarity between pediatric and adult pharmacokinetic data, and the extrapolation to pediatric patients of the demonstrated efficacy in adults for the 20 mg daily oral dose. Safety information was collected in Study E3810-A001-202 "Safety

and Efficacy of Rabeprazole in the Treatment of Gastroesophageal Reflux Disease in 12 to 16 Year Old Patients".

Finally, the current label only recommends the 20 mg daily dose for the treatment of symptomatic GERD in adults. In a previous chemistry supplement, the sponsor demonstrated equivalence between one 20 mg tablet and two 10 mg tablets. This was approved, but due to the concern for off-label use of an unapproved dose, the Division recommended it not be marketing at this time. In future this dose may be applicable to younger children if data demonstrate that the 10 mg dose is effective in the pediatric population.

3. Chemistry and Manufacturing

There were no new changes to the chemistry or manufacturing of this product. The carton and container labeling was reviewed by OSE. The Chemistry reviewers granted the request for categorical exclusion from providing and Environmental Assessment.

I concur with the conclusions reached by the chemistry reviewers. There are no outstanding issues.

4. Non-clinical Pharmacology/Toxicology

In response to the WR the sponsor submitted the final reports of two studies: 1.) a 5-week repeated oral dose toxicity study in neonatal rats; 2.) a 90-day repeated oral dose toxicity study in neonatal dogs.

The reviewer summarized the data as follows:

"In the 5-week oral toxicity study in the neonatal rats, E3810 was given by oral gavage to 7 days old rats at 0, 5, 25, and 150 mg/kg/day for 5 weeks. Treatment increased the serum gastrin level and stomach weight. Histopathological examination revealed a dose-related increase in cytoplasmic eosinophilia of chief cells in the stomach. The gastric mucosal thickness was also increased in the high dose males and females. The mean density of ECL cells was increased in males at 5 mg/kg or higher and females at 25 mg/kg or higher. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals."

"In the 90-day oral toxicity study in neonatal dogs, E3810 was given by oral gavage to 7 days old dogs at 0, 3, 10, and 30 mg/kg/day for 13 weeks. Treatment increased the serum gastrin level, stomach weight and gastric mucosal thickness. Histopathological examination revealed degeneration /necrosis of parietal cells and mucosal hypertrophy/hyperplasia in the fundus of the stomach in a dose related manner. The changes were reversible. Treatment did not clearly affect the physical and behavioral development of the animals."

"The 5-week oral toxicity study in the neonatal rats and the 90-day oral toxicity in neonatal dogs are acceptable and there were no new toxicities or target organ of toxicity identified in these studies as compared to the adult animals. Completion of

these studies in neonatal rats and dogs satisfied the requirements of the Pediatric Written Requests (additional information in Amendment #5 dated June 27, 2007). From a preclinical standpoint, the use of aciphex for pediatric patients of age 12-16 years is acceptable and the labeling should be revised as recommended. (See labeling contained in approval letter)"

"I concur with the conclusions reached by the pharmacology/toxicology reviewer that there are no outstanding pharm/tox issues that preclude approval."

5. Clinical Pharmacology/Biopharmaceutics

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 reviewers concluded that "Based on the PK data provided, the dosing regimen of 20 mg QD (but not 10 mg QD) is appropriate for adolescent patients aged 12-16 years in terms of efficacy."

In comparison with the adult pharmacokinetic data the reviewer drew the following conclusions:

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, $AUC_{0\text{-t}}$

Inspection of the study site was acceptable according to the DSI reviewer. Therefore, the data obtained in Study #E3810-A00-119 may be used for our determination of bio equivalence in this review.

The following labeling was proposed for the description of the pediatric pharmacokinetics of the 20 mg dose. Results for the 10 mg dose were not included at this time.

"Pediatric: 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 or seven days. An approximate 40% increase in exposure was noted following 5 to 7 days of dosing compared with the exposure after 1 day of dosing. Pharmacokinetic parameters in adolescent patients with GERD 12 to 16 years of age were within the range observed in healthy adult volunteers."

"I concur with the conclusions reached by the clinical pharmacology/biopharmaceutics reviewer and that there are no outstanding clinical pharmacology issues that preclude approval."

6. Clinical Microbiology

NA- This is an oral formulation.

7. Clinical/Statistical-Efficacy

As was mentioned above, the Written Request outlined a study in pediatric patients aged 12 to 16 years of age. The design of the study was based upon the conclusion that the efficacy of rabeprazole could be extrapolated from the adult population; the physiology and symptomatology for GERD is the same; the mechanism of action of rabeprazole is expected to be the same.

The medical reviewer outlined the issues very clearly in his review. The principle reason for not describing the "activity" data in the labeling was do to the fact that there was no placebo control arm upon which to anchor the study results. In addition, there were several analyses which were not felt to be clinically meaningful. Overall, the activity appeared to be similar to that in adults when based upon a response analysis; the absence of GERD symptoms. A more direct comparison cannot be made, as the severity of symptoms and the unit of time upon which the analyses were based was different.

The medical team concluded that base upon the extrapolation from the adult data and similarity of the pharmacokinetics in adults, the 20 mg daily dose should be approved for pediatric patients aged 12 to 16 years.

I agree with this conclusion.

8. Safety

Study E3810-A001-202 was relied upon to provide the bulk of the safety data in the pediatric patients.

The following labeling was agreed upon by the clinical review team.

"In a multicenter, open-label study of adolescent patients aged 12 to 16 years with a clinical diagnosis of symptomatic GERD or endoscopically proven GERD, the adverse reaction profile was similar to that of adults. The adverse reactions reported without regard to relationship to Aciphex that occurred in ≥2 % of 111 patients were headache (9.9%), diarrhea (4.5%), nausea (4.5%), vomiting (3.6%), and abdominal pain (3.6%). The related reported adverse reactions that occurred in ≥2 % of patients were headache (5.4%) and nausea (1.8%). There were no adverse reactions reported in these studies that were not previously observed in adults."

- **Postmarketing data:** No new safety issues.

- **Proprietary Name Review:** NA – this is not a new product, the same name as currently marketed with continue to be used.
- **Final labeling recommendations:** OSE agreed with the labeling attached to the approval letter.
- **Container Labeling Recommendations:**

[redacted]

- **REMS, Post-Marketing Requirements, Advisory Committee Meeting**

  There are no safety issues that have arisen in this application; therefore, the team does not recommend any REMS, or PMRs.

  No Advisory Committee was held for this application. The recommended action was based upon the results of a bioequivalence study and the efficacy was extrapolated from adult efficacy data due to the fact that this indication is similar in adults and pediatric patients in this age group (12 years and greater). A previous Advisory Committee was held to determine the requirement of the Written Requests for the Proton Pump Inhibitor Class. This study was a partial response to that Written Request.

9. Pediatrics

Because this is a partial response to the WR which is a PMC (post-marketing commitment) and it is not a new formulation, PREA is not applicable.

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, the sponsor still has to conduct pediatric studies covering the age range of neonates and pre-term infants (of <44 weeks of age) up to adolescents of 11 years.

10. Other Relevant Regulatory Issues

- **DSI Audits:** Satisfactory review of the clinical pharmacology study site.
- **Financial Disclosure:** form submitted and acceptable.
- **SEALD:** not consulted.

"There are no other unresolved relevant regulatory issues"

11. Labeling

- **Physician labeling:** the label was converted to the PLR format and pediatric dosing was included.
- **Carton and immediate container labels:**
- **Patient labeling/Medication guide:**
  Previously approved patient labeling was edited to include the pediatric information. No Medication Guide was recommended as necessary for this product given its safety profile by the review team.

12. Decision/Action/Risk Benefit Assessment

- **Regulatory Action:** I recommend approval of this supplement with the agreed upon labeling changes. This is in agreement with review team recommendations.

- **Risk Benefit Assessment:** Extrapolated from adults.

- **Recommendation for Postmarketing Risk Mitigation Strategy (REMS) Activities:**
  - **None**
- **Recommendation for other Postmarketing Study Commitments or Requirements:**
  - **None**

Material Reviewed/Consulted: OND Action Package	**Reviewer**
Medical Officer Review	W. Gao (6/19/08)
Medical Team Leader Review	H. Gallo-Torres (6/18/08)
Statistical Review	NA
Pharmacology Toxicology Review	K. Zhang (5/30/08)
Clinical Pharmacology Review	D. Gortler (6/20/08)
CMC Review	S. Kelly (6/13/08)
DSI Inspection BE studies	M. Seaton (6/8/08)
OSE/Division of Risk Management Review	N Carothers (6/4/08)
OSE/Division of Medication Error Prevention Review	D. Baugh (5/28/08)

OND=Office of New Drugs
OSE= Office of Surveillance and Epidemiology

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/s/

Joyce Korvick
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MEDICAL OFFICER