CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-272

PHARMACOLOGY REVIEW

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA: 21-456
Review Number: 1
Date of Submission: 1/10/02
Type of Submission: Original Indication
Information to Sponsor: Yes (x) No ( )
Sponsor: Eisai Inc.
Glenpointe Centre West
500 Frank W. Burr Blvd.
Teaneck, NJ 07660

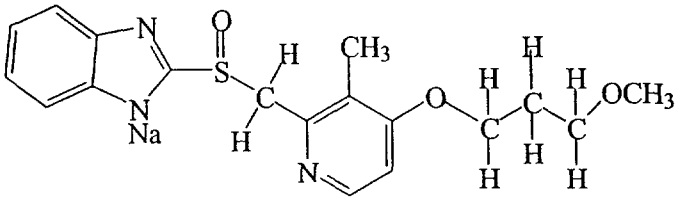
Manufacturer: Eisai Co. Ltd.
——— Japan

Reviewer Name: Stephen G. Hundley, Ph.D., DABT
Pharmacology Reviewer
Division: Special Pathogen and Immunologic Drug Products
HFD-590

Review Completion Date: 10/15/02

Drug:

Trade Name: Aciphex™
Generic Name: Rabeprazole sodium
Chemical Name: 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl] sulfinyl]-1*H*-benzimidazole sodium
CAS #: 117976-90-6
Molecular Formula: $C_{18}H_{20}N_3NaO_3S$
Molecular Weight: 381.4
Molecular Structure:



Relevant INDs/NDAs: INDs ——— NDA 20-973

Drug Class: Gastric parietal cell H^+/K^+ -ATPase proton pump inhibitor.

PHARMACOLOGY/TOXICOLOGY COVER SHEET

Indication: Eradication of *Helicobacter pylori* in the treatment of peptic ulcers and gastritis in combination therapy with amoxicillin and clarithromycin.

Clinical Formulation: Enteric coated tablet.

Route of Administration: Oral

Proposed Use: Triple therapy consisting of 20 mg rabeprazole (bid), 1000 mg amoxicillin (bid), and 500 clarithromycin (bid) for durations of 7 or 10 days.

EXECUTIVE SUMMARY

Recommendations:

Approvability – The NDA submission is approvable from the perspective of nonclinical pharmacology and toxicology.

Nonclinical Studies – Additional studies were requested as a Phase IV commitment to further evaluate the relationship between the rabeprazole/ amoxicillin/clarithromycin dosing regimen and hindquarter paralysis observed in female rats in a four-week toxicity study and to conduct a four-week oral toxicity study in beagle dogs with an appropriate rabeprazole/amoxicillin/clarithromycin dosing regimen.

Labeling – The sponsor's proposed label is acceptable with regard to the nonclinical pharmacology and toxicology portions of the label.

Summary of Nonclinical Findings:

The nonclinical data package submitted to the Division of Gastrointestinal and Coagulation Drug Products (HFD–180; NDA 20-973, March 31, 1998) supported clinical trials that included daily 40 mg rabeprazole doses for periods of 4 to 8 weeks as therapy for gastroesophageal reflux disease and 40 mg daily for 6 weeks as therapy for gastric ulcers. The Pharmacologist's Review of the definitive nonclinical pharmacology/toxicology studies for NDA 20-973 was completed on 12/18/98. Aciphex™ (rabeprazole) is currently approved for treatment of gastroesophageal reflux syndrome, duodenal ulcers, gastric ulcers, and Zollinger Ellison Syndrome. The

nonclinical pharmacology/toxicology data package submitted under NDA 20-973 was sufficient to support indications and clinical trials of longer duration than that currently proposed for eradication of *Helicobacter pylori*. Therefore, the previously submitted pharmacology/toxicology reports are sufficient for supporting seven to ten days of rabeprazole dosed at a 40 mg total daily dose (20 mg, bid). The dose levels and duration of dosing for amoxicillin and clarithromycin are also consistent with currrently approved dosing regimens for both drugs.

The original submission (IND- ——) to support rabeprazole triple therapy (rabeprazole/amoxicillin/clarithromycin) for *Helicobacter pylori* contained nonclinical toxicology studies in rats with mixtures of the these compounds. These studies were entitled:

> **A Single Oral Dose Toxicity Study of Combination Treatment of E3810, Amoxicillin, and Clarithromycin in Rats, Report S98618.**
>
> **A Single Oral Dose Toxicity of Combination Treatment of E3810 and Amoxicillin or E3810 and Clarithromycin in Rats, Report S98624.**
>
> **A 4–Week Oral Repeated Dose Toxicity Study of Combination Treatment of E3810, Amoxicillin, and Clarithromycin in Rats, Report S98012**

No mortality resulted following single doses of rabeprazole (250 or 500 mg/kg) in combination with amoxicillin (2000 mg/kg) and clarithromycin (1000 mg/kg). The most notable clinical observation was mydriasis in female rats and resulted from the rabeprazole/amoxicillin (250 or 500/2000 mg/kg) combination and not from rabeprazole plus clarithromycin. All clinical signs were resolved by Day 4 post-dosing.

The 4-week repeat dose toxicity study in rats utilized constant amoxicillin and clarithromycin dose levels (1000 and 50 mg/kg, respectively). The amoxicillin/clarithromycin combination with rabeprazole dose levels of 1 and 5 mg/kg resulted in toxicological effects associated only with amoxicillin and clarithromycin. The dosing regimen of rabeprazole at 25 mg/kg with amoxicillin plus clarithromycin resulted in hindquarter paralysis in female rats during the second week of dosing. Hindquarter paralysis or other serious clinical effects were not observed in 3-month oral toxicity studies with rabeprazole dose levels as high as 300 mg/kg (based upon the Pharmacology Review of nonclinical studies submitted to NDA 20-973). The amoxicillin/clarithromycin dosing regimen (absent rabeprazole) did not produce hindquarter paralysis. Histopathology of female rats sacrificed *in extremis* revealed atrophy of thigh muscle fibers and bone marrow hypoplasia. No histopathology was observed in central and peripheral nerve tissue from these rats.

Gross necropsy of female rats sacrificed *in extremis* also revealed thymic atrophy and histopathological analysis detected cortical atrophy of the thymus. Similar thymic effects were observed in male and female rats receiving daily *iv* 25 or 50 mg/kg doses of rabeprazole over 4 weeks (cited in the Pharmacology Review of the NDA 20-973 submission). All of the clinical effects observed in surviving female rats from the 25 mg/kg rabeprazole plus amoxicillin/clarithromycin dosing routine were reversible by Day

29 after dosing was discontinued on Day 24. Additional toxicological effects seen in the 4-week study, such as enlarged cecums and clinical chemistry changes, were associated amoxicillin and clarithromycin and not with rabeprazole.

Female rats from the rabeprazole/amoxicillin/clarithromycin (25/1000/50 mg/kg) dose level that were sacrificed *in extremis* lost 22 to 29 percent of their body weight from the timepoint of final body weight gain (Day 11 to Day 15) to the last body weight determination prior to the *in extremis* sacrifice. The observed hindquarter paralysis was consistent with muscle fiber deterioration due to the overall poor condition of the animals. Additionally, the surviving females exhibited an average 7 percent body weight depression between the timepoint of final body weight gain and removal of the dosing regimen on Day 24. These data suggest that rabeprazole in conjunction with amoxicillin and clarithromycin enhanced the sensitivity of rats to the general toxicological effects of amoxicillin and clarithromycin. In general, rats are especially sensitive to the gastrointestinal effects of antibiotics due to alteration in the normal intestinal microflora.

The following additional toxicity studies were requested of the sponsor as a Phase IV commitment (letter to the sponsor dated 5/10/02).

> A four-week oral toxicity study in rats that extensively evaluates the dose response relationship between rabeprazole, amoxicillin, and clarithromycin and hindquarter paralysis.
>
> A four-week oral toxicity study in beagle dogs with an appropriate rabeprazole/amoxicillin/clarithromycin dosing regimen to determine if the hindquarter paralysis observed in rats is also seen in dogs and also to provide a nonrodent species for general toxicological observations.

No additional Pharmacology/Toxicology NDA Review is provided beyond the Cover Sheet and Executive Summary.

/S/

Stephen G. Hundley, Ph.D., DABT
Pharmacology/Toxicology Reviewer
Division of Special Pathogen and Immunologic Drug Products (HFD-590)

Concurrence: /S/

Kenneth Hastings, Dr. P.H., DABT
Pharmacology/Toxicology Supervisor & Team Leader
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/s/

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