CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020973

PHARMACOLOGY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 13, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

SUBJECT: NDA 20,973 (Aciphex/Rabeprazole Sodium) -
Mutagenic Effects - Pharmacology Concerns About
Safety of Long Term Use in Humans - Recommendations

TO: NDA 20,973

Rabeprazole sodium was tumorigenic (gastric ECL Cell Carcinoids) in female Sprague-Dawley rats even at the lowest tested dose (5 mg/kg or 30 mg/m^2, 2 times the recommended human dose based on body surface area). Rat gastric ECL cell proliferative lesions are not entirely due to hypergastrinemia. Other factors may also be responsible. Rabeprazole sodium and its demethylated metabolite were mutagenic in Ames test. Rabeprazole sodium was also mutagenic in mammalian cell (CHO cell/HGPRT and mouse lymphoma cell L5178Y/$TK^{+/-}$) forward mutation tests.

For the aforementioned reasons, from a preclinical standpoint, there is a continuing concern about the safety of long term human use of ACIPHEX in nonpathological conditions. The potential risk in long term use needs to be further assessed. It is the prevailing opinion in the CDER Pharmacology/Toxicology Community (CAC) that further evaluation of genotoxic carcinogens as rabeprazole sodium and other available drugs of the same class in $p^{53+/-}$ transgenic mouse may more directly assess the role of genotoxicity in the carcinogenic response and could provide information of value to the assessment of risk for long term use in humans. Accordingly, the sponsor was requested via a

teleconference on July 21, 1999 to conduct a 26-week carcinogenicity study of rabeprazole sodium in heterozygous $p^{53\ (+/-)}$ transgenic mice with a preceding 4-week dose-ranging study in C57BL/6 mice as phase 4 program. The sponsor agreed to such a phase 4 commitment.

/S/

Jasti B. Choudary, B.V.Sc., Ph.D.

cc:
NDA
HFD-180
HFD-181/CSO, Ms. Walsh
HFD-180/Dr. Choudary
HFD-180/Dr. Zhang
HFD-103/Dr. Raczkowski

JBC/hw/8/13/99
C:\MSWORD\PHARM\N\20973908.0JC

APPEARS THIS WAY
ON ORIGINAL

CSO/Walsh

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 29, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

APR 29 1999

SUBJECT: NDA 20,973 (ACIPHEX) - Sponsor's Revised Draft Labeling (Amendment Dated March 5, 1999)

REFERENCE: Regulatory Project Manager's (Ms. Walsh) Review Dated April 21, 1999.

TO: NDA 20,973

The following comments address the changes in the preclinical portions of the sponsor's revised draft labeling. The numbering of the comments corresponds to the numbers in Ms. Walsh's review:

3. PHARMACODYNAMICS

D. Effect on ECL cells - The change is acceptable.

6. PRECAUTIONS

D. Carcinogenesis, Mutagenesis, Impairment of Fertility

I. The editorial change of [redacted] is acceptable.

II. Change of highest dose in Sprague-Dawley rat carcinogenicity study from [redacted] is acceptable.

III. Inclusion of males in ECL cell hyperplasia is acceptable.

IV. The changes proposed by the sponsor for the mutagenesis paragraph are not acceptable. The paragraph should start with the positive tests as in the "approvable labeling of 1/29/99". In the second sentence the results of the ex vivo (sponsor calls it in vivo/in vitro) UDS test may be added. Thus the sentence should read:

V. The last sentence about the fertility and reproductive performance test should remain as a separate paragraph as in "approvable labeling of 1/29/99".

E. Pregnancy, Teratogenic Effects etc.
The editorial change of is acceptable.

/S/

Jasti B. Choudary, B.V.Sc., Ph.D.

cc:
NDA 20,973
HFD-180
HFD-181/CSO, Ms. Walsh
HFD-180/Dr. Choudary

JBC/hw/4/29/99
C:\MSWORD\PHARM\N\20973904.0JC

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 13, 1999

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products
HFD-180

SUBJECT: NDA 20,973 (ACIPHEX) - Changes in Preclinical Portions of Labeling as per Dr. DeGeorge's Comments.

TO: NDA 20,973

The following changes in the preclinical portions of the labeling accommodate Dr. DeGeorge's suggestions. They are indicated by the page and line numbers of the "A-3 LABELING: FDA REV" of the action package. Only the recommended human dose for GERD was used in computations.

Page 8, Lines 177-188 "Effects on Enterochromaffin-like (ECL) cells"

[redacted]

2 Page(s) Redacted

DRAFT LABELING

NDA 20,973 **Review #1**

Sponsor & Address: Eisai Inc.
Teaneck, New Jersey

Reviewer: Ke Zhang, Ph.D.
Pharmacologist

DEC 18 1998

Date of Submission: Original - March 31, 1998
Amendment - October 21, 1998

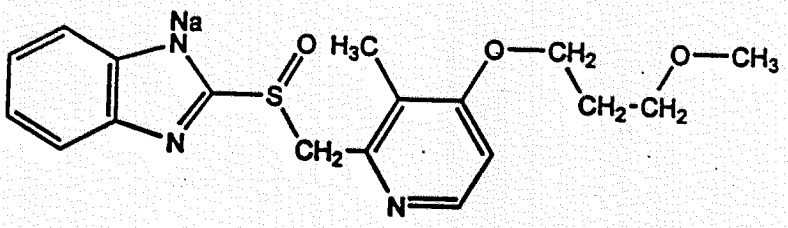
Date of HFD-180 Receipt: Original - April 3, 1998
Amendment - October 21, 1998

Date of Review: December 16, 1998

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Original Summary

DRUG: Rabeprazole sodium / Aciphex / E3810 / LY307640,
Delayed release tablet

2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]methyl]sulfinyl]-benzimidazole sodium



Molecular Formula: $C_{18}H_{20}N_3NaO_3S$ MW: 381.43

CATEGORY: Gastric parietal cell H^+/K^+-ATPase (proton pump) inhibitor.

Related INDs: IND [redacted]

Marketing Indications and Dose: Aciphex is used for treatment of erosive or ulcerative gastroesophageal reflux disease (GERD), gastric and duodenal ulcers and pathological hypersecretory conditions including Zollinger-Ellison syndrome. The recommended adult oral dose is 20 mg daily for up to 4 weeks (healing of duodenal ulcers) [redacted] and 8 weeks (healing of erosive or ulcerative GERD). For long-term maintenance of healing of erosive or ulcerative GERD, the recommended adult dose is 20 mg/day. This represents a total daily dose of 0.4 mg/kg/day if 50 kg body weight assumed. For patients with pathological hypersecretory conditions including Zollinger-Ellison syndrome, the recommended adult oral dose is 60 mg/day. The dose should be adjusted to individual patient needs and should be continued for as long as clinically indicated.

PRECLINICAL STUDIES AND TESTING LABORATORIES:

Type of Study	Study #	Lot #	Lab	Review Page #
Pharmacology				
Absorption, Distribution, Metabolism And Excretion				7-15 15-41
Mice	S96614 S96615 CHE726/17			
Rats	CHE726/16 SHKA950221 SHKA950201 19961676 T93046 F-10 / W-19961539 F-4 / W-19961211 F-8 / W-19961158 F-13 / W-19940654 F-15 / 19940597 T93009 920516 T92038 W-19961530 W-19961531 W-19961137 W-890497			
Rabbits	870531			
Dogs	CHE726/14 F-16 / w-19940600 F-10 / w-19961539 F-18 / w-19940655 F-19 / HRC/ESI/02/921621 W-19961202			
Protein binding study (in vitro)	W-19961245			
Protein binding study (ex vivo/in vitro)	W-19961533			
Distribution of 14C-E3810 to blood cells	W-19961224			
Study of interaction with human liver cytochrome p-450	Report # 1			
Acute Toxicity				
E3810, oral and i.v. in mice	881222	87092101	1	41
E3810, oral and i.v. in rats	881212	87092101	1	41
E3810 enantiomers, i.v. in rats	931214	93033101	1	42
Degradation products, oral and i.v. in rats	921312	93032901 52113001 A2060205 11052222	1	42-43
Degradation product BCPP, oral in rats	S98613	12061208 18022410	1	42-43
E3810, oral in dogs	871246	87092101	1	41

Subacute/Subchronic/Chronic Toxicity				
13-week oral study in mice	EIS014/3810	89010911	2	80-81
2-week i.v. study in rats	952111	14062301	1	43-46
4-week i.v. study in rats	882113	87052701	1	46-47
13-week oral study in rats	872113	87052701	1	47-50
3-month oral study in rats	R31193	13051304	3	103-108
6-month oral study in rats	R00895	13051304	3	54-57
1-year oral study in rats	EIS012/0348	89010911 89120401 14062301	2	50-54
2-week i.v. study in dogs	952141		1	57-59
13-week oral study in dogs	872142	K751802 K751803 87042201	1	60-63
13-week oral study in dogs	872145		1	63-65
1-year oral study in dogs	EIS013/0648	K990701, K990702 K041900, K051100	2	65-68
1-year oral study in dogs	D00394	CT02521, CT02522 CT02871, CT02867	3	68-73

1 = Department of Drug Safety Research, Eisai Co., Ltd, Gifu, Japan
2 = [redacted]
3 = [redacted]

Type of Study	Study #	Lot #	Lab	Review Page #
Special Toxicity				
Antigenicity study in mice	896122	89010911	1	74
Antigenicity study in guinea pig	886161	88020601	1	73-74
Antigenicity study in guinea pig	896165	89010911	1	74
Antigenicity study in rats and dogs	886011/886041	----	1	75
2-week pharmacokinetic study in rats	T93009	11042522	1	76-77
2-week pharmacodynamic study in rats	T93008	11042522	1	95-98
Relationship between plasma gastrin level and ECL proliferation	900415	90060702	1	77-79
Carcinogenicity				
88/104-week oral (gavage) study in CD-1 mice	92/EIS015/0039	89010911 89120401 90060702 11042522 89010911 89120401	2	82-87
104-week oral (gavage) study in F-344 rats	91/EIS011/1215	90060702 11042522 14031803 15113004	2	88-94
104-week oral (gavage) study in Sprague-Dawley rats	R00995, R01095	16072403 16041603	3	99-117

Reproductive Toxicity				
Segment I i.v. fertility and reproductive toxicity study in rats	1079	89010911 89120401	4	118-120
Segment II oral teratology study in rats	884212	88020601	1	126-128
Segment II i.v. teratology study in rats	R00295	13051304	3	120-126
Segment II i.v. teratology study in rabbits	884232	88020601	1	129-131
Segment III i.v. pre- and postnatal reproductive toxicity study in rats	3049	89120401	4	131-132

1 = Department of Drug Safety Research, Eisai Co., Ltd, Gifu, Japan
2 =
3 =
4 =

Type of Study	Study #	Lot #	Lab	Review Page #
Mutagenicity				
Tests for E3810				
Ames test	897102	630824	1	132-133
Ames test	930818AMS3736	12070203	3	133-134
Ames test	930914AMS3736	12070203	3	134-135
Ames test	930809AMS3736	12070203	3	135
Ames test	930827AMS3736	12070203	3	136
In vitro chromosome aberration tests	897402	89010911	3	145
Mammalian Cell (CHO/HGPRT) Forward mutation assay	930811CHO3736	12070203	1	147-150
Mouse lymphoma cell (L5178Y/TK$^{+/-}$) Forward Mutation assay at tk locus	930921MLA3736	12070203	3	151-152
Mouse lymphoma cell (L5178Y/TK$^{+/-}$) Forward Mutation assay at tk locus	931012MLA3736	12070203	3	154-155
Mouse micronucleus test	897223	89010911	3	146
In Vitro unscheduled DNA synthesis in rat hepatocytes	930805UDS3736 930810UDS3736	12070203	3	146-147
Ex Vivo unscheduled DNA synthesis in rat hepatocytes	16278-0-494	13051304	5	153-154
Test for metabolites				
Ames test	897105	T87793-43 T87793-37-A T87793-58 T89497-8 T87793-42-A T88090-43-1 T88090-50	1	139-143
Ames test (demethylated metabolite)	931221AMS3755 940111AMS3755	93092702	3	137-138
Ames test (demethylated metabolite)	931214AMS3755	93092702	3	136-137
Ames test (carboxylic acid metabolite)	897503	T88090-43-2 T88090-50	1	143-144
Ames test (degradation product, CEBI)	S98607	04669-977291	1	144
Ames test (degradation product, BCPP)	S98611	04669-975081	1	144-145

1 = Department of Drug Safety Research, Eisai Co., Ltd, Gifu, Japan
3 =
5 =

Following studies were previously submitted to IND 33,985: **(1)** pharmacology, **(2)** ADME, **(3)** acute toxicity studies in mice, rats, and dogs, **(4)** 13-week oral toxicity studies in mice, rats and dogs, **(5)** 4-week i.v. toxicity study in rats, **(6)** 3-month and 6-month oral toxicity studies in rats, **(7)** 1-year oral toxicity studies in rats and dogs, **(8)** special toxicity studies, **(9)** 88/104-week oral carcinogenicity study in CD-1 mice, **(10)** 104-week oral carcinogenicity study in F-344 rats, **(11)** Segment I i.v. fertility and reproductive toxicity study in rats, **(12)** Segment II oral teratology study in rats, **(13)** Segment II i.v. teratology study in rabbits, **(14)** Segment III i.v. pre- and postnatal reproductive toxicity study in rats, **(15)** Ames tests (parent compound and metabolites), **(16)** in vitro chromosome aberration tests, **(17)** mammalian cell (CHO/HGPRT) forward mutation assay, **(18)** mouse lymphoma cell (L5178Y/$TK^{+/-}$) forward mutation assays at tk locus, **(19)** unscheduled DNA synthesis in rat hepatocytes (in vitro and ex vivo), and **(20)** mouse micronucleus test. These studies were previously reviewed by Dr. Ching-Long Joseph Sun (initial submission) and Dr. Tanveer Ahmad (amendments # 023, 029, 036, 038, 041, 050, 051, 064, 068, 072, 081, 084, 090, 095, 096, 101, 114, 117). These reviews are reproduced in the appropriate portion of the present review. In addition, new studies submitted in the present NDA and NDA amendment dated October 21, 1998 have been reviewed below.

PHARMACOLOGY:

Rabeprazole is a substituted benzimidazole proton pump inhibitor. It inhibits H^+/K^+-ATPase activity on the surface of gastric parietal cells and thus blocks the final step of the gastric acid secretion. Its pharmacological activities were characterized in a number of *in vitro* and *in vivo* Preparations.

Primary Activity

In Vitro:

1. Inhibition of H^+/K^+-ATPase (isolated from porcine gastric mucosa) by E3810 and Omeprazole: E3810 and omeprazole concentration dependently inhibited H^+/K^+-ATPase activity in vitro with IC_{50} values of 2.6×10^{-7}M and 2.8×10^{-6}M respectively. Data indicated that E3810 is 10 times more potent than omeprazole in this experiment.

2. <u>In Vitro Effects of Histamine, Cimetidine (H_2 blocker) and E3810 on Collagen Syntheses</u>: In rat fetal fibroblasts culture (which actively produce collagen), histamine (10^{-8} - 10^{-4}M) stimulated collagen synthesis (maximum stimulation = about 18% over the control value), while cimetidine (10^{-7} - 10^{-3}M) concentration dependently inhibited histamine-stimulated collagen synthesis (data presented graphically). E3810 (10^{-8} - 10^{-4}M) had no significant effect on histamine stimulated collagen synthesis in this experiment.

3. <u>In Vitro Inhibitory Activities of E3810 and its Metabolite, E3810-Thioether Against H. Pylori</u>: E3810, E3810-thioether, omeprazole, omeprazole-thioether and lansoprazole-thioether had potent antibacterial activity against 15 strains of H. pylori. The activity of E3810 was about 16 times higher than that of omeprazole and activity of E3810-thioether was about 32 times higher than that of omeprazole.

Compounds	MIC_{90} (μg/ml) Against 15 Strains of H. Pylori
E3810	3.13
E3810-thioether	1.56
Omeprazole	50
Omeprazole-thioether	25
Lansoprazole-thioether	25

4. <u>Inhibitory Actions of Metabolites and Decomposed Compounds of E3810 on H^+/K^+-ATPase (in vitro)</u>: E3810 and desmethyl metabolite of E3810 concentration dependently inhibited H^+/K^+-ATPase activity (isolated from pig gastric mucosa) in vitro with IC_{50} values of 2.0×10^{-7}M and 2.9×10^{-7}M respectively. Data indicated that E3810 and desmethyl-E3810 were equipotent in this experiment. In this experiment inhibitory activities of other metabolites of E3810 (thioether-E3810, sulfone-E3810, desmethyl-thioether-E3810 and carboxylic-E3810) and its decomposition products ("CEBI and SHBI") were negligible at 3×10^{-5}M.

5. Inhibition of Acid Secretion in Isolated Rabbit Gastric Glands: Acid secretion in isolated rabbit gastric glands was stimulated by db-cAMP. E3810 and omeprazole (low concentrations: 3-5x10^{-7}M) inhibited db-cAMP stimulated acid secretion (data presented graphically),. however this inhibition was reversed with time in E3810 treated system, while inhibition persisted for at least 180 min in omeprazole treated system. In another experiment, E3810 and omeprazole inhibited db-cAMP stimulated acid secretion in isolated rabbit gastric glands with IC_{50} values of 0.16 and 0.36 μM respectively. Addition of GSH (1-3 mM) in the incubation mixture reverses the antisecretory activity of E3810 and omeprazole.

6. Inhibition of H^+/K^+-ATPase (Isolated from Fundic Mucosa of Pig Stomach) by E3810 and Its Optical Isomers (Report # E-1-19): In vitro (±)-E3810 (racemic mixture), (R)-(+)-E3810 [R-(+) enantiomer] and S-(-)-E3810 [S-(-) enantiomer] concentration dependently inhibited H^+/K^+-ATPase activity with IC_{50} values of 0.28, 0.30 and 0.30 μM respectively. The data indicated that all three compounds were equipotent with respect to inhibition of H^+/K^+-ATPase activity.

In Vivo:

1. Effects of E3810 and Famotidine on Gastric Acid Secretion in Rats: E3810 and famotidine (histamine [H_2] receptor blocker) both dose dependently inhibited basal acid secretion in rats (ID_{50}: E3810 = 3 mg/kg, famotidine = 0.3 mg/kg).

2. Effects of E3810 and Famotidine on Histamine Stimulated Gastric Acid Secretion in Rats: Both E3810 and famotidine dose-dependently inhibited histamine-stimulated gastric acid secretion in rat with ID_{50} values of 1 mg/kg and 0.3 - 1 mg/kg respectively. It should be noted here that inhibitory activity of E3810 on histamine-stimulated gastric secretion was more potent than on basal acid secretion, while famotidine inhibitory activity was similar in basal as well as histamine-stimulated gastric acid secretion in rats (see above).

3. Effect of E3810 on Histamine-Stimulated Gastric Acid Secretion in Acute Fistula Rats: E3810 dose-dependently inhibited histamine-stimulated gastric acid secretion in acute fistula rats (87% inhibition at 10 mg/kg).

4. Effects on Urinary Excretion of Gastrin and Histamine and Histamine Content and Histidine Decarboxylase (HDC) Activity in Rat Fundic Tissue: Both E3810 or omeprazole (20 mg/kg for 2 weeks) significantly increased urinary gastrin (59-269%) and histamine (20-174%) excretion, histamine content (57-89%) and HDC activity in the fundic tissue of rat. In this experiment omeprazole was more potent than E3810 (data presented graphically).

5. **Effects of E3810 and Famotidine (H_2 blocker) on Water-immersion Restraint Stress Ulcer in Rats**: Both E3810 and famotidine dose-dependently inhibited stress-induced ulcer formation in the gastric mucosa of rat. The maximum inhibition of ulcer formation was 98% at 30 mg/kg of E3810, while 30 mg/kg of famotidine only produced 66% inhibition in this model. The data indicated that E3810 is more potent than famotidine in this model.

6. **Effects of E3810 and Famotidine on HCl/Ethanol-Induced Ulcer in Rats**: In rats, gastric ulcers were induced by HCl/ethanol. Pretreatment with E3810 (100 mg/kg, oral) completely protected rats from HCl/ethanol induced gastric ulcers. In this model famotidine was ineffective.

7. **Effects of E3810 on Healing of Acetic Acid-Induced Gastric Ulcers in Rats**: In rats, gastric ulcers were produced by applying 0.07 ml of 100% acetic acid to "serosal surface" of gastric wall for 60 sec. Rats were treated subcutaneously with E3810 (3 or 30 mg/kg) or omeprazole (30 mg/kg) for 11 days. Gastric ulcers were reduced in size by 49% and 58% at 3 and 30 mg/kg of E3810 respectively (30 mg/kg of omeprazole produced 21% reduction in ulcer size).

8. **Effects of E3810 Metabolites (Desmethyl-E3810 and Thioether-E3810) on Histamine-Induced Gastric Acid Secretion in Chronic Gastric Fistula in Dogs**: Desmethyl-E3810 (0.5 mg/kg) and thioether-E3810 (2 mg/kg) both inhibited histamine-induced gastric acid secretion in chronic gastric fistula dogs (inhibition at 1 hr post dose: 47% and 41% respectively).

Inhibition of pentagastrin-stimulated acid secretion in dogs with a chronic gastric fistula (Report W-890394): Both compounds were administered intraduodenally through a tube positioned in the fistula, and acid secretion was stimulated by the injection of pentagastrin at 1, 24 and 48 hour afterward. For omeprazole, an additional pentagastrin challenge was conducted at 72 hours. The result is given below:

Dose	mEq acid/2 hours				
E3810	Control	1 hour	24 hours	48 hours	72 hours
0.5 mg/kg	16.82±2.66	8.10±1.65	15.85±2.90	—	—
1.0 mg/kg	16.38±1.02	5.58±1.89	13.06±2.03	17.85±2.76	—
2.0 mg/kg	16.81±2.17	0.24±0.19	10.17±1.20	14.17±2.36	—
4.0 mg/kg	16.81±2.17	0±0	10.14±1.18	18.60±2.36	—
Omeprazole	Control	1 hour	24 hours	48 hours	
0.5 mg/kg	16.82±2.66	6.74±1.44	13.58±1.08	—	—
1.0 mg/kg	16.38±1.02	4.7±2.39	12.11±3.15	14.73±3.30	—
2.0 mg/kg	16.81±2.17	0.13±0.09	6.11±1.26	12.42±1.47	18.34±1.78
4.0 mg/kg	16.81±2.17	0.04±0.02	5.76±1.15	11.51±2.42	17.93±2.81

Both drugs inhibited acid release in a dose-dependent manner with omeprazole being slightly higher. Furthermore, omeprazole may have a longer duration of action than E3810 at doses higher than 0.5 mg/kg at 24 and 48 hours after administration of drug.

Inhibition on histamine-stimulated acid secretion in dogs with an indwelling gastric fistula (Report W-890392): One hour after intravenous administration of histamine either compound was given intraduodenally. Both compounds caused dose and time dependent decrease in acid secretion. The ED_{50} for inhibition of histamine-induced gastric acid secretion was 0.06 mg/kg for E3810 and 0.112 mg/kg for omeprazole at the time of maximal inhibition (1 hours post-treatment). To test duration of action, the animals were given a second and third challenges with histamine 24 and 48 hours after the drugs (0.5 mg/kg of E3810 or 1.0 mg/kg of omeprazole) has been given, secretion was still significantly inhibited in the animals treated with omeprazole as shown below:

Treatment	Time after drug	Mean gastric acid secretion (mEq/hour) ± SE
Control	---	25.92±4.33
E3810 (0.5 mg/Kg)	1-2 hours	0±0
	24-25 hours	16.1±3.34
	48-49 hours	21.0±4.08
Omeprazole (1 mg/Kg)	1-2 hours	0±0
	24-25 hours	9.89±2.27*
	48-49 hours	13.23±2.29*
	72-73 hours	18.54±3.37

* $p < 0.05$

The results may indicate that omeprazole exhibited longer anti-secretaory action than that of E 3810. However, dose levels were different between two compounds. A definitive conclusion can not be reached.

Inhibition of pentagastrin-induced gastric acid secretion in dog after one week of daily intraduodenal treatment (Report W-890391): Both omeprazole (0.5 mg/kg) and E3810 (0.25 mg/kg) inhibited acid secretion during the drug-administration period. Inhibition by omeprazole was still evident at day 8 indicating longer anit-secretory action. The result is given below: