RECOMMENDATION:

From a preclinical standpoint, this NDA is approvable. Sponsor should be asked to revise the labeling as recommended.

/S/ 12/16/98
Ke Zhang, Ph.D.

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Zhang
HFD-345/Dr. Viswanathan
HFD-180/Dr. Gallo-Torres
R/D Init.: J. Choudary 11/13/98

KZ/hw/12/7/98 & 12/16/98
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① Concur with the exception of the following.

② a. 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/m², 2 times the recommended human dose based on body surface area). It is also the consensus opinion that regulation of rat gastric ECL cell growth is multi factorial (The Toxicology Forum / Aspen Colorado, July 1997 and not necessarily dependent on gastrin alone.

b. Rabeprazole sodium was also mutagenic in microbial (Ames / Salmonella) and mammalian cell (CHO cell / HGPRT & Mouse lymphoma cell L5178Y/TK +/-) mutagenicity tests.

c. For the aforementioned reasons, from a preclinical standpoint, approval of ACIPHEX for long term use in non-pathological conditions is not recommended.

/S/ 12/18/98

ATTACHMENTS:

Appendix I: Tumor and Non-tumor data for 88/104 week carcinogenicity study in mice.
Pages 168 - 216

Appendix II: Tumor and Non-tumor data for 104 week carcinogenicity study in rats.
Pages 217 - 244

Appendix III: Tumor and Non-tumor data for 104 week carcinogenicity study in rats
Pages 245 - 261

94 Page(s) Redacted

RAW DATA

Statistical Review and Evaluation (Carcinogenicity Studies)
Addendum

NDA: 20-973

Date: **Dec. 15, 1998**

Applicant: Eisai Research Institute

DEC 15 1998

Name of Drug: Aciphex (rabeprazole sodium) Tablets

Documents Reviewed:

Original NDA volume dated 8/3/1998.

I. Introduction

A report of statistical review and evaluation of the mouse and rat carcinogenicity studies of this NDA was issued by the Division of Biometrics on Nov. 5, 1998. However, some information stated in the sections of Background and Reviewer's Summary need to be corrected.

II. Corrected Background

The Background section in the report of the statistical review and evaluation, dated 11/5/98, should be changed to the following.

In this NDA submission, four two-year carcinogenicity experiments in both mice and rats were included. Two of the four experiments were Study# EIS/011 in CD-1 mice and Study# EIS/015 in F-344 rats. [redacted] conducted the two experiments for the sponsor [redacted] also statistically analyzed the data from the two experiments. FDA reviewed the two experiments previously and concluded that only mouse study was acceptable. Since [redacted] was the sponsor for this NDA submission, FDA requested [redacted] to conduct the Sprague-Dawley rat study for further assessment on the compound toxicity.

The other two experiments were in Sprague-Dawley rats. They were Study# R00995 and Study# R01095, of male and female rats, respectively. The two experiments were intended to assess the carcinogenic potential of [redacted]307640 Sodium in the oral gavage of Sprague-Dawley rats when administered orally using some selected dose level.

This report contains only the results of statistical review of the last two experiments in Sprague-Dawley rats.

III. Correction for Reviewer's Summary

The word "diet" in the first paragraph of the Reviewer's Summary should be changed to "oral gavage". The modified paragraph is presented below. Based on the results of the sponsor's survival and tumor data analyses and this reviewer's evaluation on the validation of the study design, the assessments with regard to the carcinogenic potential of LY307640 Sodium in the "oral gavage" of Sprague-Dawley rats are summarized below.

/S/

Wen-Jen Chen, Ph.D.
Mathematical Statistician

Concur: Dr. Sankoh /S/

Dr. Karl Lin /S/ 12/15/98

cc:
Archival : **NDA:** 20 - 973 Aciphex (rabeprazole sodium) Tablets

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Statistical Review and Evaluation
(Carcinogenicity Studies)

NDA: 20-973

Date: **Nov. 5, 1998**

Applicant: Eisai Research Institute

Name of Drug: Aciphex (rabeprazole sodium) Tablets

NOV - 5 1998

Documents Reviewed:

Original NDA volume dated 8/3/1998.

I. Background: In this NDA submission, four two-year carcinogenicity experiments in both mice and rats were included. Two of the four experiments were Study# EIS/011 in CD-1 mice and Study# EIS/015 in F-344 rats. conducted the two experiments for the sponsor. also statistically analyzed the data from the two experiments. FDA reviewed the two experiments previously and concluded that they were not valid studies.

The other two experiments were in Sprague-Dawley rats. They were Study# R00995 and Study# R01095, of male and female rats, respectively. The two experiments were intended to assess the carcinogenic potential of /307640 Sodium in the diet of Sprague-Dawley rats when administered orally using some selected dose level.

This report contains only the results of statistical review of the last two experiments in Sprague-Dawley rats.

II. The rat study

IIa. Design

Two separate experiments, one in male (Study# R00995) and one in female (Study# R01095) rats, were conducted over a period of 24 months.

Study R00995 consisted of six treatment groups: two identically untreated control groups and four compound-treated groups known as low, medium I, medium II, and high with targeted doses 5, 15, 30, and 60 mg /307640/kg, respectively. Each treatment group utilized seventy males and all animals were singly caged.

Study R01095 consisted of seven treatment groups: two identically untreated control groups

and five compound-treated groups known as low, medium I, medium II, high I, and high II with targeted doses 5, 15, 30, 60, and 120 mg [redacted]307640/kg, respectively. Each treatment group utilized sixty females and all animals were singly caged.

IIb. Sponsor's analysis

Survival data analysis:

The sponsor tested the heterogeneity of survival distributions between groups using the survival analysis methods described by Cox (Regression models and life tables, Journal of the Royal Statistical Society, B, 34, 187-220, 1972). In addition, dose-related increasing trend in mortality was tested using the method by Tarone (Tests for trend in life table analysis, Biometrika 62:679-682, 1975). Since there were two control groups in each study, two sets of statistical analyses were performed: one on the two control groups and the other on all compound-treated groups with a pooled control group. Both Cox's two-sided tests and Tarone's one-sided tests were conducted at the significance level of 0.05.

Results for male rats (Study# R00995)

Based on the analysis results, the sponsor indicated that not only a significant difference in the mortality rates was found between the two control groups ($p=0.02$) but also a significant increasing trend was detected ($p<0.001$) in the mortality rates of the pooled control and the compound-treated groups (low, medium I, medium II. , and high dose groups). However, upon removal of medium II and high dose groups, the significant trends were not present ($p=0.47$).

The survivals of male rats at week 80, week 90, and at the end of 104 weeks for control 00, control 01, low, medium I, medium II, and high groups were 73%, 64%, 74%, 61%, 40%, and 30% at week 80; 53%, 37%, 50%, 41%, 26%, and 27% at week 90; and 21%, 9%, 24%, 11%, 4%, and 11% at the end of week 104.

Further evaluations of the mortality data were performed by excluding all tumor-related deaths and reanalyzing for the increasing trends in the mortality rates of the pooled control, low, medium I, medium II, and high dose groups. The sponsor indicated that the increasing trends were shown significant in the pooled control and compound-treated groups up to high ($p<0.001$) and up to medium II ($p=0.005$) dose groups. However, no significant linear positive trend was detected in the pooled control, low, and medium I dose groups.

Finally, based on the above analysis results, the sponsor concluded that doses of 30 and 60 mg/kg (medium II and high dose groups) had exceeded the MTD (Maximum Tolerated Dose) in males.

Results for female rats (Study# R01095)

The sponsor's analysis indicated that no significant difference in the mortality rates was found between the two control groups ($p=0.211$). However, a significant increasing trend ($p=0.006$) was detected in the mortality rates of the pooled control and compound-treated groups (low, medium I, medium II, high I, and high II dose groups). Similar to the result for male rats, the significant trend was not present ($p=0.28$) after removal of high II dose group.

The survivals of female rats for control 00, control 01, low, medium I, medium II, high I, and high II groups at week 80, week 90, and end of 104 weeks were 85%, 87%, 90%, 93%, 78%, 75%, and 65% at week 80; 65%, 63%, 77%, 63%, 67%, 63%, and 50% at week 90; and 47%, 33%, 52%, 28%,40%, 43%, and 22% at the end of week 104.

Further evaluations of the mortality data were performed by excluding all tumor-related deaths and reanalyzing for the increasing trends in the mortality rates of the pooled control, low, medium I, medium II, high I, and high II dose groups. The sponsor indicated that a significant increasing trend was present ($p<0.001$) in the pooled control, and compound-treated groups up to high II dose group. However, upon removal of high II dose group, no significant linear positive trend was detected.

Finally, based on the above analysis results, the sponsor concluded that the dose of 120 mg/kg (high II) had exceeded the MTD in females.

Tumor data analysis:

The sponsor performed the trend tests on tumor incidence rates using the method described by Peto et al. (Guidelines for sample sensitive significance test for carcinogenic effects in long-term animal experiments, Long term and short term screening assays for carcinogens: A critical appraisal, International agency for research against cancer monographs, Annex to supplement, World Health Organization, Geneva, 311-426, 1980). The method of randomization trend tests were used for those site/tumor combinations with low tumor incidence. The sponsor analyzed malignant and benign tumors separately and excluded site/tumor combinations with occurrences not greater than two from the statistical analysis. In addition, the sponsor also conducted homogeneity tests between two control groups using Chi-Square analysis method. Peto's trend test for a positive linear trend in incidence rates was conducted at the significance levels of 0.025 and 0.005 for rare and common tumors, respectively.

Results from tumor data analysis of male rats

For male rats, the sponsor performed the dose-related increasing trend tests on data of individual tissue/tumor combinations in the following four ways:

1. malignant tumor incidence data for the pooled control, low, and medium I dose groups;
2. benign tumor incidence data for the pooled control, low, and medium I dose groups;
3. malignant tumor incidence data for the pooled control, low, medium I, medium II, and high dose groups; and
4. benign tumor incidence data for the pooled control, low, medium I, medium II, and high dose groups;

The sponsor emphasized that no statistically significant increasing trends or heterogeneity were detected in the tumor incidence rates for both malignant and benign tumors either excluding or including medium II and high groups.

Results from tumor data analysis of female rats

As in the case for male rats, the sponsor performed the dose-related increasing trend tests on data of individual tissue/tumor combinations in the following four ways:

1. malignant tumor incidence data for the pooled control, low, medium I, medium II, high I, and high II dose groups;
2. benign tumor incidence data for the pooled control, low, medium I, medium II, high I, and high II dose groups;
3. malignant tumor incidence data for the pooled control, low, medium I, medium II, high I, and high II dose groups; and
4. benign tumor incidence data for the pooled control, low, medium I, medium II, high I, and high II dose groups;

The sponsor's results from analysis of tumor data of female rats showed that tumor types Stomach/Carcinoid Malignant ($p=0.006$), Stomach/Carcinoid Benign ($p<0.001$), and Stomach/Carcinoid Combined ($p<0.001$) were found to have positive linear trends using data from pooled control, low, medium I, medium II, high I, and high II dose groups. However, the significant positive trend in Stomach/Carcinoid malignant tumor disappeared when data of high II group were excluded.

In addition, the sponsor also indicated that for both tumor types Stomach/Carcinoid Benign and Combined, the dose-related increasing trends were significant in compound-treated groups not only up to high II dose group ($p<0.001$ for both tumor types) but also up to high I dose group ($p=0.001$ for Stomach/Carcinoid Benign and $p<0.001$ for Stomach/Carcinoid Combined), up to medium II dose group ($p=0.001$ for Stomach/Carcinoid Benign and $p<0.001$ for Stomach/Carcinoid Combined), and up to medium I dose group ($p=0.007$ for both tumor types).

The incidence rates and p-values of the above tumor types are presented below.

Female Rats

Organ/Tumor Name	Tumorf[1]	C1&C2	Low	Med-I	Med-II	High-I	High-II	p-Value
Stomach/Carcinoid	M	0	0	0	1	1	2	0.006*
Stomach/Carcinoid	B	0	1	3	5	4	5	<0.001*
Stomach/Carcinoid	C	0	1	3	6	5	7	<0.001*

1: Tumor Type Flag - M for Malignant Tumor; B for Benign Tumor; C for Combined Tumor.
***: a significant positive linear trend detected based on the division's p-value adjustment rule.**

Finally, based on sponsor's results in Table H28 to Table H31, no significant heterogeneity was found at significance level of 0.05 between the two control groups in the tumor types tested.

IIc. Reviewer's comments

Because the sponsor's analysis was based on the statistical methodologies used by the Division of Biometrics for survival and tumor data and no unusual results are observed, this reviewer did not perform further statistical analysis on the survival and tumor data for male and female rats.

The sponsor claimed that the high dose groups (medium II and high for males; high II for females) were over MTD, and that data of those groups should not be included in the statistical analysis. However, Dr. Choudary (pharmacology review team leader in HFD-180) recommended a statistical analysis of tumor incidence rates using data sets from two control groups and five compound-treated groups.

To validate sponsor's claim, this reviewer evaluated the validity of the rat study design.

Evaluation on the validity of the rat study design

Usually, an evaluation on the validity of a carcinogenicity study is performed when it is a negative study. However, the criteria used in the evaluation can also be used to evaluate the sponsor's claim that the high doses in the rat study were over MTD.

Before drawing the conclusion that the high dose groups (medium II and high dose groups for male rats; high II dose group for female rats) exceeded MTD, it is necessary to look into the following two issues pointed out in the paper by Haseman (Statistical issues in the design, analysis and interpretation of animal carcinogenicity studies, Environmental Health Perspectives, Vol. 58, pp 385-392, 1984):

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumor ?

(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (Issues in carcinogenicity testing: Dose selection, Fundamental and Applied Toxicology, Vol. 5, pp 66-78, 1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics II/OEB/CDER, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would be considered as a sufficient number and adequate exposure.

In addition, Chu, Cueto and Ward (Factors in the evaluation of 200 national cancer institute carcinogen bioassay, Journal of Toxicology and environmental Health. Vol. 8, pp 251-280, 1981), suggested that " To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the MTD. In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy.

i) " A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."

ii) " The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."

iii) " In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

We will now investigate the validity of the Sprague-Dawley rat carcinogenicity study, in the light of the above guidelines.

The following summarizes the survival data for male rats in the medium II and high dose groups and for female rats in high II dose group.

	End of 52 weeks	End of 78 weeks	End of 92 Weeks	End of 104 weeks
Male	(93%/89%)[#]	(44%/43%)	(23%/27%)	(6%/11%)
Female	93%[!]	67%	48%	23%

[#]: (survival rate of medium II /survival rate of high dose groups in male rats);
[!]: survival rate of high II dose group in female rats.

From the above summary of survival data and the survival criteria mentioned above, it might be concluded that there were enough rats living long enough and being exposed for a sufficient amount of time to the drug.

The following summarizes data for body weight gains for the rat study.

		Mean body weight(gms)			
Sex	Group	Day -1 of study	End of study	Weight gain	Percentage of Pooled-Control
Male	Pool.-Cntrl.[#]	222.19	556.29	334.1	
	Low	224.40	503.24	278.84	83.4
	Medium I	222.29	512.63	290.34	86.9
	Medium II	224.19	593.67	369.48	110.6
	High	221.80	506.63	284.83	85.26

Mean body weight(gms)

Sex	Group	Day -1 of study	End of study	Weight gain	Percentage of Pooled-Control
Female	Pool.-cntrl.#	187.62	425.23	237.61	
	Low	184.58	416.31	231.73	97.5
	Medium I	187.28	390.82	203.54	85.66
	Medium II	184.48	426.24	241.76	101.75
	High I	188.57	397.96	209.39	88.12
	High II	186.02	391.31	205.29	86.40

#: Pooled-Control group.

Therefore, relative to the pooled-control, male rats had an incremental weight gain equal to 10.6% (110.6% - 100%) in the medium II group and a decrement weight gain in the high dose group equal to 14.74% (85.26% - 100%); female rats had a decrement weight gain in the high II dose group equal to 14.60% (86.4% - 100%).

The mortality rates at the end of the experiment are as follows:

Sex	Pooled-Control	Medium II (Male rats)	High (Male rats)	High II (Female rats)
Male	85%	94%	88.57%	
Female	59%			77%

From the results of the above analysis of the body weight gain and mortality data of the rat study, this reviewer concluded that the dose levels for the medium II and high groups for the male rats were not over MTD; and that the level for the high II group for female rats was over MTD due to the group's significantly higher mortality and relatively large weight gain decrement. However, before concluding that the MTD was not exceeded other clinical signs and histopathological effects should also be taken into consideration.

III. Reviewer's Summary

Based on the results of the sponsor's survival and tumor data analyses and this reviewer's evaluation on the validation of the study design, the assessments with regard to the carcinogenic potential of LY307640 Sodium in the diet of Sprague-Dawley rats are summarized below.

Survival data analysis results

For male rats, not only a significant difference in the mortality rates was found between the two control groups ($p=0.02$) but also a significant increasing trend was detected ($p<0.001$) in the mortality rates of the pooled control and the compound-treated groups (low, medium I, medium II, and high dose groups).

For female rats, no significant difference in the mortality rates was found between the two control groups ($p=0.211$). However, a significant increasing trend ($p=0.006$) was detected in the mortality rates of the pooled control and compound-treated groups (low, medium I, medium II, high I, and high II dose groups).

Tumor data analysis results

Using the criteria for evaluating the validity of experimental designs of negative studies proposed by experts in the field, it might be concluded that the dose levels for medium II and high dose groups for male rats were not over MTD; and that the dose level for the high II dose group for female rats was over the MTD. However, before concluding that the high doses in male rats are close to MTD other clinical signs and histopathological effects shall also be taken into consideration. Based on the results of this evaluation of the validity of the study, the following significant findings in tumor data analysis were obtained.

For male rats, no statistically significant increasing trends (on the basis of Division's p-value adjustment rule) or heterogeneity were detected in the tumor incidence rates for both malignant and benign tumors either excluding or including the data of medium II and high dose groups.

For female rats, based on the Division's p-value adjustment rule for the positive linear trend test, tumor types Stomach/Carcinoid Benign ($p<0.001$), and Stomach/Carcinoid Combined ($p<0.001$) were found to have positive linear trends using data from pooled control, low, medium I, medium II, high I, and high II dose groups. The increasing trends in these two tests stayed significant in the tests after dropping data of high II dose group, of high II and high I groups, and of high II, high I, and medium II groups. However, under significance level of 0.05, no significant heterogeneity was found between the two control groups.

/S/

Wen-Jen Chen, Ph.D.
Mathematical Statistician

Concur: Dr. Sankoh /S/

Dr. Karl Lin /S/ 11/5/98

cc:

Archival : **NDA**: 20 - 973 Aciphex (rabeprazole sodium) Tablets

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