The placebo and ranitidine healing rates, both at 4 and 8 weeks, were very significantly less than for rabeprazole 20 mg/day ($p<0.001$). Even though the numbers were relatively small in Study I, the difference between the other rabeprazole doses of 10 and 40 mg/day were also significantly better than placebo at both time points ($p<0.001$). There was no significant difference between the doses of rabeprazole in Study I, nor between the rabeprazole 20-mg/day rates in the two studies I and J. Significant improvement in heartburn severity and frequency was also seen.

Comment: Study I was called a "dose-ranging" study, but insufficient numbers of patients were enrolled to have any reasonable power to distinguish between rabeprazole doses. It was powered just to show superiority of all three doses over placebo. It was not, therefore, a study designed to find the best dose of rabeprazole. The lowest dose, 10 mg/day, actually looked slightly better at both 4 and 8 weeks, by 7 to 9%, and it clearly was of no purpose to increase the daily dose to 40 mg. To show with 80% power and $\alpha = 0.05$ (two-tailed) that 10 mg would produce 90% healing at 8 weeks and 20 mg/day only 85% would require a very large study with 685 patients per arm. In lieu of such a study, the sponsor seems simply to have declared 20 mg/day to best dose, but the decision does not appear to be based on data.

In the comparative graph above, the comparability of omeprazole and rabeprazole 20 mg/day is plotted with data from the 25 European centers other than the 2 Dutch centers, and the rate for rabeprazole 20 mg/day (53/60, 88.3% at 8 weeks) is more compatible with the North American data than the sponsor's claim of 92/100 (92%) that includes the "perfect" results in the Dutch centers.

The sponsor refers to the results of Study P, done in 27 European centers with 202 patients, as showing statistical equivalence or comparability between omeprazole 20 mg/day and rabeprazole 20 mg/day. In the proposed labeling, the sponsor wishes to include in the Clinical Studies section (Volume 1, pages 54-5) a summary of the Study P data including the Dutch data, and uses the term "comparable" to omeprazole in producing endoscopic healing.

Comment: In view of the highly unlikely results in 80 of the 202 patients, because of the exactly 20 patients on each drug studied at each of the two Dutch centers, the European data is apparently compromised and cannot be taken with confidence to support the claim that rabeprazole is "comparable to" or "equivalent to" omeprazole at the same daily dose for healing erosive esophagitis. The residual findings in the 122 other European do suggest substantially that this may indeed be so, but the single study can scarcely be called robust. It is suggested that the claim of comparability in healing be confirmed by another new study.

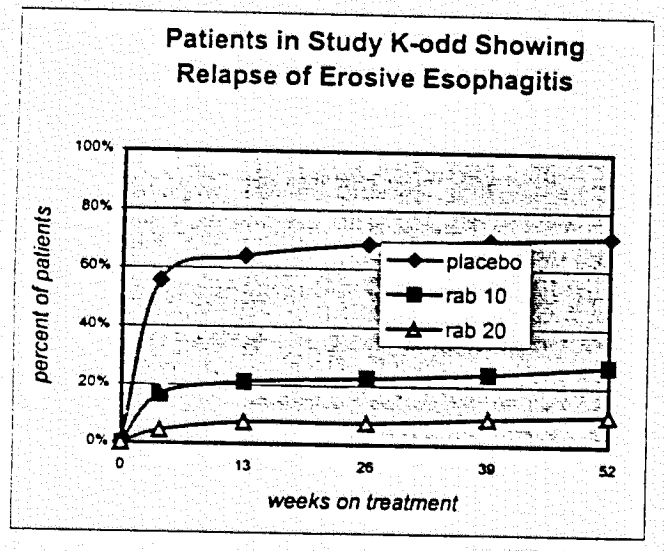
It is further suggested that the dose of rabeprazole was not well established by the small "dose-ranging" Study I, and additional work would be very desirable to determine if 10 mg/day is indeed as good as 20 mg/day for healing erosive esophagitis. To improve the study, it is suggested that it be stratified with respect to initial lesion severity, because informal analyses of the results of Studies I and J indicate that grade 4 lesion take longer to heal than grade 3 lesion, which in turn take longer to heal than grade 2 lesions. It would be quite valuable to confirm this finding, because patients with grade 4 lesions may require additional treatment time to achieve the same proportions of healing, perhaps up to 12 weeks. This would be important for clinicians to know when prescribing the treatment regimen.

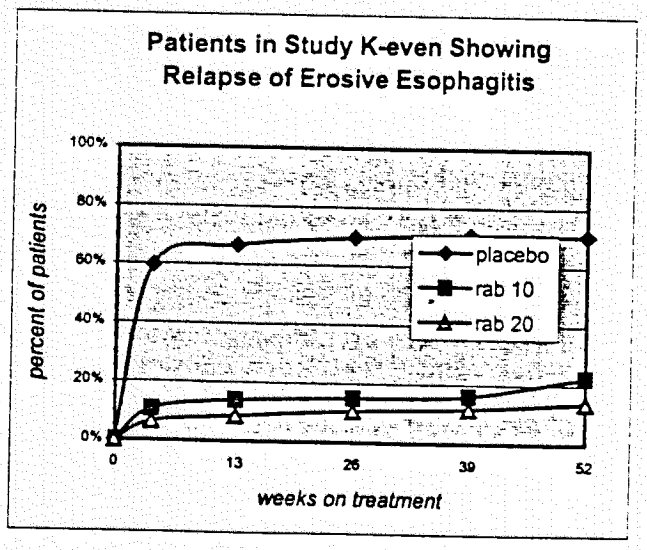
B. Maintenance of healing of erosive esophagitis

The results of Study K-odd and –even were cited in support of the superiority of rabeprazole 20 mg over placebo in reducing the relapse rate of erosive lesions after healing had been achieved. Many (162/488, 33.2%) of the patients in these studies had been previously enrolled in Study J, and were simply "rolled-over" into Study K by re-randomization on the day healing to grade 0 or 1 was seen endoscopically. However, approximately two-thirds of the patients studied in Studies K-odd and K-even were enrolled after they had healed on other therapy, outside of Study J.

Comment: It was not easy to determine from the submitted materials just what therapy had been used to heal those patients. The sponsor was asked some time ago to provide data linking the two studies, so that it could be determined which patients in Study J were randomized to which regimen in Study K. Further, the treatment used to heal the lesions if outside of Study J was also requested, but has not yet been received as of this date. It may be important to relapse tendency to know what treatment was used to heal the erosions. In the case of duodenal ulcers, relapse rates were greater for patients healed on proton-pump inhibitors than on histamine receptor-type 2 antagonists, and in turn than in those healing on antacids or simply spontaneously.

The relapse of erosive lesions was very significantly suppressed by rabeprazole, in both daily doses. As had been mentioned above, the K-odd study showed a greater benefit of 20 mg/day than 10 mg/day, but in K-even the two dose-regimens were not significantly different. The very rapid relapse of lesions when healed patients were randomized to placebo is strikingly seen in the graphs below.





The shape of the curves indicates that the incremental rate of new relapses on placebo is very rapid in the first 4 weeks off effective treatment, then slowly rises at about the same rate as seen for patients on rabeprazole. About 29% of the patients in each of the two studies did not relapse on placebo, but remained healed for the year of observation. The difference in relapse rate between either dose of rabeprazole and placebo was highly significant ($p<0.001$).

The sponsor also cites Study Q, done in 21 European centers, in support of the claim that rabeprazole is comparable or equivalent to omeprazole. It was not noted in Europe that the 20-mg daily dose of rabeprazole was superior to 10 mg. The sponsor noted that the relapse rates in Europe on both doses of rabeprazole were far lower than in the United States (at a year, the European rates of relapse were only a third as much for patients on rabeprazole 20 mg/day, and only a fifth as much for patients on rabeprazole 10 mg/day).

CUMULATIVE RELAPSE RATES IN MAINTENANCE STUDIES

Study	*week*	*rabeprazole 10 mg/day*	*rabeprazole 20 mg/day*
NRRK-odd	13	14/66 (21.2%)	5/67 (7.5%)
	52	**18/66 (27.3%)**	**7/67 (10.4%)**
NRRK-even	13	13/93 (14.0%)	8/93 (8.6%)
	52	**21/93 (22.6%)**	**13/93 (14.0%)**
NRRQ	13	1/82 (1.2%)	2/78 (2.6%)
	52	**4/82 (4.9%)**	**3/78 (3.8%)**

The sponsor explained this discrepancy by stating (Volume 1:224) that this difference "parallels disposition data which showed that a higher proportion of patients treated with 10 mg in the North American placebo-controlled trials discontinued treatment due to lack of efficacy."

Comment: The sponsor did not refer at all to the fact that at three European centers the relapse rate was zero, at the two Dutch centers and at Iceland, where 149 of the 243 patients had "perfect" responses, the same Dutch centers where perfect healing had occurred. If the denominators of the study groups in the European studies are reduced by elimination of data from sites 101, 102, and 061, then the relapse rates would become 4/30 (13.3%) for rabeprazole 10 mg/day, 3/29 (10.3%) for rabeprazole 20 mg/day, and 4/35 (11.4%) for omeprazole 20 mg/day. These results would be more consistent with the results reported in the United States for rabeprazole 20 mg/day in the combined NRRK studies, which showed 20 relapses among 160 (12.5%) patients on that dose. It would not explain the reduction by half of the relapse rate on 10 mg/day of rabeprazole in Europe.

The lack of significant difference between the 10 and 20-mg daily dose in Europe is barely noted by the sponsor in the ISE section (Volume 228:118-9). Much is made of Study-K-odd, the smallest of the three maintenance studies, although the results of Study K-even and Study Q (without Holland and Iceland) are ignored. It apparently was not thought strange that a zero relapse rate was seen in the three centers that enrolled the most patients into the study. A zero rate in 61% of the patients would have quite an impact, if it can be believed. The difference between North America and Europe cannot be explained by protocol differences, or patient selection differences, because all the studies were done with almost identical protocols.

Most of the material in the sponsor's summaries, in the ISE Volume 228 and the Summary Volume 1 tend to indicate that the dose of 20 mg rabeprazole was selected for reasons that may have more to do with marketing than with data.

V. Integrated Summary of Safety (ISS) of Rabeprazole 20 mg/day

A. Extent of exposure in these submitted studies

The sponsor has summarized the safety data for 69 submitted studies of rabeprazole, of which 63 studies had been completed as of the "cutoff" date of 31 October 1997 for the NDA submission of 31 March 1998, and 6 were continuing. These studies encompassed 5252 patients in the completed studies, 3556 of whom received rabeprazole *(Volume 249:112 and Table 1A:I6-I59, Volume 249:117-170)*. The other patients received placebo, ranitidine, or omeprazole in the erosive esophagitis healing and maintenance studies. About 368 patients in the duodenal and gastric ulcer studies received famotidine, and a few (8) healthy subjects received pirenzepine. In the continuing studies of prolonged administration of rabeprazole or omeprazole for very long-term maintenance of healing, another 809 patients were in their second or third year on treatment, and 10 more with gastric hypersecretory states were on high-dose (60 to 120 mg/day) long-term.

For the 1383 patients were the focus of this portion of the medical review, those treated for erosive esophagitis associated with GERD, the largest number, 535, received doses of 20 mg/day for up to 8 weeks for healing (294 patients) or up to a year for long-term maintenance of healing (241). Smaller numbers received ranitidine 10 mg/day for healing (27) or maintenance (247), ranitidine 40 mg/day for healing, or control drugs. These included placebo (194: 25 for healing, 169 for maintenance), ranitidine 150 mg q.i.d. (169 for healing), and omeprazole 20 mg/day (194 for maintenance). In addition, 166 patients from Study J, 72 who had healed on ranitidine and 94 who had healed on rabeprazole, continued into Study K(odd/even) for another year. An extra 431 patients started Study K *de novo*, after healing on other approved treatment regimens, for the year-long maintenance studies. From Study K, 206 patients were continuing into their second year on extended long-term treatment and observation, and 149 more into a third year. In Europe, 124 patients who had healed in Study P continued into Study Q, and were joined by 119 more who entered *de novo* after healing on standard treatments *(Volume 249:203-4)*. Of those patients, 194 continued into a second year on treatment, and 80 more into a third year (Table 3D, Volume 249:206).

In all the controlled studies of duodenal and gastric ulcer, erosive esophagitis healing and maintenance, and the gastric hypersecretory states, the median age of the 2009 patients was 52 years. They were predominantly men (1246/2009, 62%) and Caucasian (1741/2009, 87%). Some were elderly, 19% 65 to 75 years of age and 4% over 75 *(Volume 249:249)*. Of these 1064 received rabeprazole, mostly (947) 20 mg/day, and 945 received ranitidine (537), omeprazole (319), or placebo (89).

The distribution of ages for patients treated for erosive esophagitis was similar to that for all controlled studies. The mean age of the 103 patients in Study I was 50 years, the 338 patients in Study J had mean age of 51 years, 53 years in the 202 in Study P, 57 years in the 209 patients of Study K-odd, 52 years in the 288 patients of Study K-even, and 53 years in the 243 patients of Study Q.

Comment: It is important in considering rabeprazole safety to include all the patients, not just those who were investigated for erosive esophagitis. There is little reason to think that patients with duodenal ulcer or gastric ulcer would be at greater or less risk of adverse drug reactions than those with GERD complications. In a population such as this, which includes a substantial number of middle-aged and elderly persons with variably extensive prior medical histories, concurrent other medications, and risk of new problems over extended periods of time, adverse events were to be expected. It is fortunate that such extensive control groups were available for comparisons to placebo and to standard regimens of approved medications such as omeprazole and ranitidine.

B. Adverse clinical and laboratory events in these studies

The sponsor considered laboratory abnormalities discovered and reported in the North American and European controlled studies, especially proportions of patients in whom changes were seen from normal to abnormal values *(Volume 250:18-68)*. For the changes on treatment of the blood counts *(Tables 7A1 and 7A2, Volume 250:20-1; 23-4)*, tests of liver function/dysfunction *(Table 7B1 - acute healing studies and 7B2 - long-term maintenance studies, Volume 250:27-8 and 30-1)*, renal function studies *(Volume 250:34-8)*, cardiac injury tests *(pages 40-3)*, and urinalyses, there were no significant differences between patients treated with rabeprazole and with control drugs or placebo. Thyroid function testing did not reveal any rabeprazole-associated abnormalities. The serum gastrin studies (Volume 250:48) reflected only the expected dose-related increases expected of a proton-pump inhibitor (the mean rise in patients treated with omeprazole 20 mg/day (+16.8 pg/mL) was comparable to that seen in patients on rabeprazole 10 mg/day (+18.0) and less than in those on 20 mg/day (+37.4) or 40 mg/day (53.2 pg/mL). In the GERD maintenance studies in North America and Europe, there were no significant difference between rabeprazole-treated patients and those on placebo or omeprazole, with respect to changes in gastric mucosa inflammation or ECL hyperplasia.

Treatment-emergent clinical symptoms or findings were seen in most of the patients in these studies, especially in the year-long maintenance studies, but not in any consistent patterns that were different from or in excess of those in patients on placebo (if time of exposure was reckoned) or omeprazole.

Comment: In the ISS presentation, the sponsor focussed upon differences between the 10 and 20-mg/day doses of rabeprazole (Volume 250:108-173), and found no notable dose-related differences. This was consistent with the overall effort to justify the selection of the 20-mg daily dose. In the previous section (Volume 249:365-71) about 60% of the patients reported at least one treatment-emergent adverse effect, slightly more in rabeprazole-treated patients (63.5%) then in those on ranitidine (60%) or placebo (56%- but for much shorter times of exposure). It was notable that in Europe only 35% of patients on rabeprazole reported adverse events, compared to 31% in those on omeprazole. It was not clear whether this phenomenon represented selective unreporting at certain centers in Europe such as those that had such perfect results in healing and in lack of relapses.

Drug-demographic interactions were analyzed *(Volume 250:184-91)*, and disclosed no clinically significant differences in adverse events, laboratory abnormalities, or vital signs as a function of age or gender. There were too few non-Caucasians to reach conclusions on race effects, and no experience was gained for pediatric use of rabeprazole.

C. Serious adverse events in these studies

In the text for each study, we have discussed individual serious adverse events, and discontinuations because of adverse events (AEs), and deaths on or after study. The sponsor summarized all deaths, serious adverse events, and discontinuations because of adverse events up to a cut-off date of 3 February 1998, shortly before the NDA submission of 13 March 1998, in all of the completed or ongoing studies.

SERIOUS AEs AND AEs LEADING TO DISCONTINUATION FROM COMPLETED OR ONGOING STUDIES

	rabeprazole	ranitidine	omeprazole	placebo	famotidine	TOTALs
	3556	**537**	**553**	**521**	**293**	**5460**
Deaths	**7 (0.2%)**	**2 (0.4%)**	**1 (0.2%)**	**1 (0.2%)**	**0 (0%)**	**11 (0.2%)**
Serious AEs	**141 (4.0%)**	**10 (1.9%)**	**25 (4.5%)**	**11 (2.1%)**	**9 (3.1%)**	**196 (3.6%)**
Discontinuations	**108 (3.0%)**	**11 (2.0%)**	**19 (3.4%)**	**10 (1.9%)**	**15 (5.1%)**	**153 (2.8%)**

The reported deaths all appeared to be caused by malignancies or pre-existing cardiac problems, except for a patient in Japan (#16-6 in Study J081-014) who died of perforated duodenal ulcer after receiving omeprazole 20 mg/day for 2 days. Most (8) of the deaths occurred after the patients had completed study, of malignancies that presumably had been present long before they started the studies *(Volume 249:285-6)*.

The relative frequency of serious AEs while on treatment was no greater for rabeprazole than for the approved regimen of omeprazole 20 mg/day, but both agents showed somewhat more frequent AEs than famotidine, ranitidine, or placebo. The patterns of AEs reflected most often one or another pre-existing medical problem, cardiovascular, neoplastic, neurological, or other, and did not reveal a consistent type of problem that was relatively more frequent in rabeprazole-treated patients. Six patients had serious AEs even before starting the studies *(Volume 249:295)*, and 14 more after studies were completed *(Volume 249:326-8)*, none apparently caused by study drugs.

Comment: This overview corroborated the findings of the six individual studies of patients with erosive esophagitis, in which no consistent pattern of serious AEs was seen in rabeprazole-treated patients, compared to those on ranitidine or omeprazole or placebo.

The long-term, controlled studies of prolonged administration of rabeprazole 10 or 20 mg/day for a year, or even into second and third years, compared to either placebo (United States) or to omeprazole (Europe) were especially valuable. However, not very many patients were able to go long periods of time on placebo without relapsing, so there was a limit to how long the natural incidence of serious AEs could be observed in placebo-treated patients.

D. Drug-drug interactions in these studies

Rabeprazole is metabolized by the hepatic cytochrome P450 systems CYP 3A4 that convert it to sulfones and CYP 2C19 that forms the desmethyl metabolite. Although its effect at the site of pharmacodynamic action in the gastric oxyntic cells is for up to a day, its plasma half-time is only about an hour *(Volume 1:159)*. It may be expected to compete for metabolism with other compounds that share the same cytochrome systems for metabolism, and it also profoundly reduces gastric acid secretion that may affect the absorption of other drugs. Consequently, studies were done to assess the effects of rabeprazole on the absorption, distribution, metabolism, and excretion (ADME) of theophylline, digoxin, diazepam, phenytoin, warfarin, and ketoconazole. Other studies were done to assess effects of antacids and food on the pharmacokinetics of rabeprazole. These studies were not done especially for consideration of the erosive esophagitis healing and maintenance indications, but as part of the general study of this new compound.

No effects of antacids on the ADME of rabeprazole were observed in Japanese Study J081-028 *(Volume 250:174)*. Administration of rabeprazole after a meal delayed the absorption of rabeprazole, with Tmax rising from 3.6 to 5.3 hours, but did not affect the total amount absorbed, indicating that rabeprazole may be taken before or after meals with no loss of effect.

Rabeprazole decreased the bioavailability of ketoconazole by about 30% but did not appear to alter its Tmax or elimination rate (Study A001-103) in 19 healthy subjects, consistent with reduced absorption of ketoconazole from an intragastric higher pH, as observed with other proton-pump inhibitors. The pharmacokinetics of warfarin and pharmacodynamic effect on prothrombin were not affected by single or multiple doses of rabeprazole (Study A001-001) in 21 subjects. Digoxin bioavailability was increased by about 20% in 16 healthy volunteers (Study A001-102). No effect on phenytoin or theophylline phamacokinetics appeared to be caused by rabeprazole. For diazepam, rabeprazole showed less effect than omeprazole in causing increased bioavailability in extensive metabolizers of diazepam through the S-mephenytoin-4'-hydroxylase system, and tended to normalize poor metabolizers, thus showing little net effect in its interaction with diazepam.

Comment: These interaction studies are commendable but do not fully address the problems of steady state levels and effects of drugs that are taken long-term such as warfarin, digoxin, phenytoin, and theophylline, when rabeprazole is introduced for long-term use. Short-term study does not fully consider the induction of enzyme systems or changed bioavailability that may alter the critical dosage of those agents needed to maintain adequate anti-coagulation, cardiac contractility, seizure or asthma control in patients who need them. Ketoconazole and diazepam may or may not be taken at steady, long-term doses. This whole topic may require further work to elucidate critical drug-drug interactions.

In considering the huge numbers of drugs taken by patients who participated in these studies, it is suggested that analyses be made of which are most frequently taken, and whether clinical adjustments had to be made in dosing them to maintain desired clinical effects when rabeprazole was introduced.

VI. Summary of Benefits, Risks of the Proposed Formulation

The sponsor recapitulates the results of studies in support of the requested indications and dose of rabeprazole, making strong argument for the 20 mg/day dose *(Volume 277:406-411)*. It is argued that in the healing study (NRRJ) rabeprazole 20 mg/day was significantly better than the approved dose/regimen of ranitidine 150 mg q.i.d.

Comment: The sponsor does not mention that rabeprazole 10 mg/day healed erosions at least as well and somewhat better than larger doses of 20 or 40 mg/day in the "dose-ranging" Study I. No comparison was made of rabeprazole 10 mg/day versus rantidine. The justification for choosing a healing dose of 20 mg/day instead of 10 is based on the results of one of the maintenance studies, NRRK-odd, and not on acute healing data.

For maintenance of healing of erosive esophagitis, clearly both 10 and 20 mg/day of rabeprazole were far better than placebo. The finding that relapse rates were less, for both erosions and symptoms, in one of the NRRK studies (K-odd) is taken to establish the maintenance dose at 20 mg/day. It is argued that when the two studies are combined, the benefits of rabeprazole 20 mg/day are significantly greater than 10 mg/day. The include a lower relapse rate for endoscopic erosions of 20/160 (12.5%) instead of 39/159 (24.5%), and lower rates for return of heartburn of worsened severity night or day, and of increased frequency. Deaths and serious AEs, although none were considered possibly or probably related to study medication, were not less on the lower dose, discontinuations because of adverse events were almost the same in both dose groups, and treatment-emergent adverse effects were only slightly less on the lower dose of 10 mg/day than on 20 mg/day.

Relapse Rates	*rabeprazole 10 mg/day*	*rabeprazole 20 mg/day*	*Odds Ratio 10/20 (C.I.)*
Esophageal erosions	39/159 (24.5%)	20/160 (12.5%)	2.36 (1.29, 4.34)
Heartburn frequency	52/127 (40.9%)	41/124 (33.1%)	1.51 (0.88, 2.58)
Daytime severity	22/148 (14.9%)	13/149 (8.7%)	1.93 (0.92, 4.06)
Nighttime severity	32/141 (22.7%)	19/148 (12.8%)	2.19 (1.15, 4.18)
Deaths	0/274 (0%)	0/266 (0%)	
SAEs related	0/274 (0%)	0/266 (0%)	
Total SAEs	27/274 (9.9%)	25/266 (9.4%)	
AE discontinuations	16/274 (5.8%)	13/266 (4.9%)	
Severe AEs	40/274 (14.6%)	43/266 (16.2%)	
Moderate AEs	114/274 (41.6%)	119/266 (44.7%)	
Mild AEs	157/274 (57.3%)	163/266 (61.3%)	
All AEs	193/274 (70.4%)	199/266 (74.8%)	
Gastrin >149 pg/mL	36/152 (23.7%)	60/155 (38.7%)	
ECL hyperplasia	12/159 (7.5%)	43/266 (16.3%)	

The greater effect of the higher dose on serum gastrin levels and ECL hyperplasia were noted, but discounted as indicating that the 20-mg daily dose is "providing a greater level of gastric acid suppression" rather than as a potential safety problem.

Comment: Although repeated and enthusiastic arguments are made for establishing 20 mg/day as the dose of rabeprazole, this neglects that fact that the dose-ranging study was too small to show any difference between doses, and that 10 mg/day was at least as good in that small Study I. There has in fact not been any true dose-ranging done. The superiority of the 20-mg/day dose for maintenance was really shown in only the smallest of three studies, NRRK-odd, and not in NRRK-even or in NRRQ done in Europe. Although the dose of 20 mg of rabeprazole does truly work well, and is significantly better than either placebo or ranitidine for healing, and far better than placebo for maintenance, it has not been proved to be THE best dose.

The sponsor's summary *(Volume 277:412)* asserts that rabeprazole 20 mg every morning was shown to be "equivalent" to omeprazole 20 mg/day in healing erosive and ulcerative esophagitis. No comment was made concerning equivalence of the two agents in long-term maintenance of healing *(Section 2.1, "Long-Term Treatment (GERD Maintenance)", Volume 277:406-411).*

Comment: The several concerns about the credibility of the European Studies P and Q have been mentioned and elaborated in the text above. Although the data from the residual patients of Study P, after setting aside the questionable data from the two Dutch sites, do indicate that rabeprazole and omeprazole in equal doses of 20 mg/day have comparable effects, the power of the study to detect a difference if one truly existed was diminished greatly by removal of 80 of 202 patients. The likelihood that 20 patients in sequence on each randomized drug would all have exactly the same erosion score initially and all would heal precisely in 4 weeks to grade 0 is vanishingly small. It is even less credible that a second site would produce exactly the same results. It is even further of concern that those two sites had zero relapse rates in the maintenance Study Q. It may or may not be true that omeprazole and rabeprazole are clinically equivalent at equal doses in the healing and maintenance of healing, but the studies are badly compromised, and should be well confirmed by a new study in which we could have more confidence.

There were some observations that emerged from the data that deserve further investigation. It was noted that in the acute healing studies the rates of healing were dependent on the severity of the initial erosive lesions, the grade 4 lesions showing significantly lower healing rates at week 4 than the grade 3 lesions, which in turn were lower than the grade 2 lesions. The results at week 8 were less different, but still evident. Because no patients were treated for 12 weeks, it is not possible to say if those with initial grade 4 lesions would heal if treated for longer. The severity issue appears strong enough to justify stratification before randomization, if additional studies of healing are to be done. The concept that one dose is proper for all patients for all indications seems more a concept for easy marketing than a thoughtful guide to treating individual patients.

An idea that comes from experience with duodenal ulcer relapse, in the days before the importance of Helicobacter pylori (Hp) infections was widely realized, is that the tendency to relapse is not the same in all patients, and those who require greater gastric acid suppression in order to heal will be those who more frequently and quickly relapse when that acid suppression is stopped. In GERD and erosive esophagitis, it still may be possible that patients who heal spontaneously or on placebo are less likely to show relapse than those who require H2-blockers or proton-pump inhibitors or higher doses of proton-pump inhibitors to heal.

VII. Regulatory Recommendations

The data from these studies very convincingly demonstrate the great superiority of rabeprazole 10 or 20 mg/day over placebo and over the approved dose/regimen of ranitidine in healing the erosive esophageal lesions associated with GERD, and over placebo for maintenance. It is recommended that the dose of rabeprazole 20 mg/day be approved for these indications:

1) A regimen of 20 mg/day of rabeprazole for 4 or 8 weeks is safe and effective for **healing** erosions/ulcerations of the esophagus associated with GERD. Reduction in heartburn frequency, and the severity of daytime and nighttime heartburn have also been demonstrated.

2) For **maintenance** of healing and reducing the relapse rate of erosions/ulcerations in patients with already healed lesions or erosive esophagitis associated with chronic GERD, and for reduction in relapse rates of heartburn symptoms in these patients, a daily dose of rabeprazole 20 mg for a year is safe and effective.

3) Superiority over rantidine 150 mg q.i.d. for healing may be claimed

4) It is not recommended that the requested claim of equivalence of rabeprazole 20 mg/day to omeprazole 20 mg/day, either for healing or maintenance of healing, be approved, because of serious concerns and questions about the validity of the data from European Studies P and Q.

It should be noted that the optimal dose of rabeprazole for healing erosive esophagitis was not established, and a more thorough and convincing comparison of 10 and 20 mg/day of rabeprazole should be done. The sponsor also did not note that the extent/severity of the initial esophageal lesions had a very important effect on the healing rates. These items are suggested to be included in the design of a confirming study. It is not suggested that additional placebo or ranitidine control groups would be needed, but rabeprazole 10 mg/day and 20 mg/day should be compared to omeprazole 20 mg/day in the confirming study of healing and maintenance of healing in patients stratified by severity of their initial esophageal erosive lesions.

/S/ 30 Nov 98

John R. Senior, M.D., Medical Officer . date
Division of Gastrointestinal & Coagulation Drug Products

cc:
NDA 20-973
HFD-180
HFD-180/LTalarico /S/ 12-3-98
HFD-180/HGallo-Torres
HFD-180/RPrizont
HFD-180/MFan
HFD-180/EDuffy
HFD-180/JChoudary
HFD-181/BStrongin

Concur. November 30, 1998
/S/

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DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS

MEDICAL TEAM LEADER'S REVIEW

ACIPHEX™ (Rabeprazole)

SAFETY UPDATE

DEC 22 1998

NDA:	20-973
Submission Date:	October 21, 1998
Sponsor:	Eisai Inc.
Route of Administration:	Oral (tablets)
Pharmacological Category:	Antisecretory/Antiulcer Inhibitor of the (H^+,K^+)-ATPase enzyme (proton pump) of the parietal cell in the gastric mucosa

INDICATIONS AND DOSAGE

Healing of Erosive of Ulcerative Gastroesophageal Reflux Disease

- 1X20 mg tablet once daily for up to 8 weeks

Long-term Maintenance of Healing of Erosive or Ulcerative GERD

- 1X20 mg tablet once daily for up to 4 weeks

[redacted]

Treatment of Pathological Hypersecretory Conditions Including Zollinger-Ellison Syndrome

- starting dose is 60 mg once a day, to be adjusted to individual patient needs for as long as clinically indicated

Material Reviewed:	This submission consists of 24 volumes: volume 1 had been electronically paginated whereas volumes 2-24 contain manually paginated Appendices. Pertinent CRFs were provided in volumes 22-24
Reviewer:	Hugo E. Gallo-Torres, M.D., Ph.D.