

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020973

MEDICAL REVIEW(S)

AUG 19 1999

DEPUTY OFFICE DIRECTOR'S MEMORANDUM TO THE FILE

NDA: 20-973

Drug: Aciphex (rabeprazole sodium) Delayed-Release Tablets

Applicant: Eisai, Inc.

Submission Date: 5 March 1999

PDUFA Goal Date: 3 September 1999

Memo Completed: 19 August 1999

The original NDA for rabeprazole was submitted on 3 March 1998, and an approvable action was taken on 29 January 1999. A resubmission of the application was made on 5 March 1999.

Rabeprazole is a substituted benzimidazole that suppresses gastric acid secretion by inhibition of the H⁺/K⁺-ATPase, which is located on the secretory surface of gastric parietal cells. Rabeprazole shares structural and pharmacological similarities to two proton-pump inhibitors that are marketed in the United States, omeprazole and lansoprazole.

Because rabeprazole sodium degrades in acidic media, Aciphex Delayed-Release Tablets are enteric-coated to allow the drug to traverse the stomach. After oral administration and absorption, the drug is bound extensively to plasma proteins (~96%). Rabeprazole is metabolized in the liver, primarily to a sulphone metabolite (by cytochromes P450 3A) and to a thioether metabolite (by reduction). It is also metabolized by cytochrome P450 2C19 to a desmethyl derivative. The plasma half-life of an orally administered 20 mg dose is approximately 1 to 2 hours. The inhibition of the gastric proton-pump is prolonged much longer than would be predicted by plasma drug levels.

In humans, rabeprazole sodium inhibits both basal and stimulated gastric-acid output, and decreases intragastric acidity. In patients with gastroesophageal reflux disease (GERD), the drug decreases esophageal acid exposure. As expected, repeated administration of rabeprazole increases fasting gastrin levels.

For reasons summarized in the Division Director's memorandum, Aciphex is being approved for four indications on the basis of adequate and well-controlled clinical studies:

- Healing of erosive or ulcerative gastroesophageal reflux disease. The recommended oral dose is 20 mg taken once daily for four-to-eight weeks. Patients who have not healed after eight weeks may receive a repeated course of treatment.
- Maintenance of healing of erosive or ulcerative gastroesophageal reflux disease. The recommended oral dose is 20 mg taken once daily.

- Healing of duodenal ulcers. The recommended oral dose is 20 mg taken once daily after the morning meal for up to four weeks. Although most patients heal within four weeks, patients who have not healed may receive additional therapy.
- Treatment of pathological hypersecretory conditions, including Zollinger-Ellison Syndrome. The recommended starting oral dose is 60 mg taken once daily. Depending on clinical response, the dose may be titrated or split into divided doses. Oral doses up to 100 mg q.d. and 60 mg b.i.d. have been administered, and some patients were treated continuously for up to one year.

In general, except as noted above for the hypersecretory conditions, daily oral doses of 40 mg did not confer substantially more clinical benefit than daily oral doses of 20 mg for these conditions. Although the pharmacokinetics of rabeprazole were evaluated in single- and multiple-dose studies of patients with mild-to-moderate hepatic impairment, the drug has not been studied in patients with severe hepatic impairment.

As specified in the approvable letter date 29 January 1999, Aciphex has not been granted an indication []

The applicant has three outstanding phase-4 commitments:

- []
- The approved labeling states that the safety and effectiveness of rabeprazole in pediatric patients have not been established. The approval letter contains standard language to remind the applicant to provide pediatric use information (63 FR 66632 and 21 CFR 314.55) and also alerts the applicant to the possibility of seeking pediatric exclusivity (under section 505A of the Federal Food, Drug, and Cosmetic Act).
- An adequate and well-controlled study examining the effect of food on the bioavailability of rabeprazole.
The approved labeling states that the effects of food on the absorption of rabeprazole have not been evaluated.
- A 26-week carcinogenicity study in heterozygous p53(+/-) transgenic mice. The dose selection for this study should be based on a 4-week dose-range finding study in

C57BL/6 mice. The high dose for the carcinogenicity study should be the maximum tolerated dose (MTD) determined on toxicity-based endpoints.

As reflected by this last phase-4 commitment, one of the principal safety concerns for rabeprazole is that the drug is tumorigenic and mutagenic. Like the marketed drugs omeprazole and lansoprazole, rabeprazole administration to rats caused gastric neuroendocrine cell tumors to develop (tumorigenicity). Specifically, in a two-year carcinogenicity study both malignant and benign gastric enterochromaffin-like (ECL) cell carcinoids were found in female Sprague-Dawley rats at the lowest dose of rabeprazole that was evaluated (5 mg/kg or 30 mg/m²).

Thus, caution is merited if rabeprazole is to be administered to patients long-term. However, the relevance of this finding of carcinoid tumors in rodents has uncertain clinical significance and was discussed at previous FDA Advisory Committee meetings. Moreover, both omeprazole and lansoprazole have been marketed in the United States for several years (i.e., omeprazole was first approved for use in the United States in September 1989 and lansoprazole was approved in May 1995) and the drugs have been administered to millions of people. In this experiential data base, no clear association with human gastric tumors has yet been identified for these drugs. Finally, proton pump inhibitors are currently the best pharmacologic therapy for erosive esophagitis, which is associated with significant morbidity.

Unlike omeprazole and lansoprazole, however, rabeprazole is mutagenic. The drug was positive in both non-mammalian and mammalian assay systems (i.e., the Ames Salmonella typhimurium assay, CHO/HGPRT forward-mutation assay, and the in vitro mouse lymphoma cell assay). The demethylated metabolite of rabeprazole was also mutagenic in the Ames test. Thus, additional caution for the long-term administration of rabeprazole to humans is merited. Accordingly, the applicant has agreed to the 26-week p53(+/-) transgenic mouse study. Moreover, the National Center for Toxicologic Research (NCTR) will likely perform an additional mutagenicity assay: a one-year study in which neonatal mice will receive doses of rabeprazole, omeprazole, and lansoprazole during the period of rapid gastric cell proliferation. Depending on the results of these studies, additional restrictions may be placed in the labeling of these products, additional long-term epidemiological studies may be considered, and/or additional regulatory actions may be initiated.

In conclusion, Aciphex appears to be safe and effective when used as specified for the indications noted above. Caution is merited if rabeprazole is to be administered to patients over a long period of time.

 /S/ 8/19/99
Victor F.C. Raczkowski, M.D., M.S.

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

DATE: DEC 22 1998

FROM: Hugo E. Gallo-Torres, M.D., Ph.D., Medical Team Leader (MTL),
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
and
Lilia Talarico, M.D., Director
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Rabeprazole sodium (ACIPHEX™)¹, NDA 20-973 (Eisai Inc.):
Recommendations for Regulatory Action

TO: Victor Rackowski, Acting Director
Office of Drug Evaluation III

I. INTRODUCTION

Rabeprazole (RABE) is a substituted benzimidazole derivative that suppresses gastric acid secretion by specific inhibition of the H⁺/K⁺-ATPase enzyme system. Because this enzyme is regarded as the acid (proton) pump within the parietal cell of the stomach, RABE has been characterized as a gastric proton-pump inhibitor (PPI). Like other PPIs, such as omeprazole (PRILOSEC®) and lansoprazole (PREVACID®), RABE blocks the final step of gastric acid secretion and produces dose-related sustained inhibition of both basal and stimulated gastric acid secretion:

Gastric Acid Parameter	RABE (20 mg QD)	PL	p-value
Basal Acid Output ^a	0.4	2.8	<0.01
Stimulated Acid Output ^b	0.6	13.3	<0.01
Time Gastric pH >3 (%)	65	10	<0.01
a,b, mmol/h			

The effects of the drug on acid secretion in healthy volunteers and in patients in whom the drug would be indicated, are as expected of a PPI. In healthy volunteers, RABE substantially increased intragastric pH after 7 days of dosing, and significantly inhibited intragastric acidity, with no substantial advantage at 40 over 10 or 20 mg. In patients with gastroesophageal reflux disease (GERD), at doses of 20 or 40 mg daily for 7 days, RABE reduced the reflux time for up to 8 days, the number of reflux episodes, and the number of reflux episodes >5 minutes as well

¹ ACIPHEX™ is sometimes referred to in the pharmacological literature as E3810 or LX307640

as increased mean gastric pH. There were no differences between the two dose levels in their effectiveness within these parameters.

Also, as expected of PPIs, RABE produces a dose-related increase in the median fasting serum gastrin level, while the group median values remain within normal range. Other expected effects are ECL cell hyperplasia in rats and mice, and gastric carcinoids in rats. [Approved PPIs, omeprazole and lansoprazole, display the same pre-clinical effects.] Furthermore, experimental studies with *H. pylori* have shown that, just as omeprazole and lansoprazole, RABE is bacteriostatic – but not bactericidal – on some *H. pylori* strains.

RABE is available for oral administration as delayed-release, enteric-coated tablets containing 10 or 20 mg of RABE sodium². RABE delayed-release tablets are enteric-coated. This allows the drug, which, like other PPIs, is acid labile, to pass through the stomach intact. In gastric parietal cells, RABE is protonated, concentrated, and transformed to an active sulfenamide. The sustained inactivation of the H⁺/K⁺ ATPase is reflected by the above-mentioned long PD action compared to the short PK half-life (approximately one hour).

II. REVIEWERS

RABE is similar in chemical structure and pharmacological activity to omeprazole³ and lansoprazole⁴ (approved PPIs) and to pantoprazole (an experimental PPI presently under review).⁵ Through their submission in NDA 20-973, Eisai is requesting approval for the marketing of ACIPHEX™ for several indications associated with gastric acid inhibition. The assessment of evidence of efficacy and safety of RABE, presented by the sponsor for each indication, was carried out by Medical Officers/Scientist reviewers specified in Table 1.

In the present memorandum, approval/not approval of the drug for a specified indication is recommended taking into account, fundamentally, the primary MO's reviews and Recommendations for Regulatory Action, in conjunction with those of the statistician. Included for each indication are a summary of the assessment of study results submitted by the sponsor in support of that indication and a clear justification for the regulatory action recommended. Also included are brief statements regarding the safety of the drug in specified patient populations. Assessment of the overall safety of the drug is carried out in two additional documents: review

² Inactive ingredients are mannitol, OH-propyl cellulose, magnesium oxide, low-substituted OH-propyl cellulose, Mg stearate, ethyl cellulose, OH-propyl methycellulose phthalate, diacetylated monoglycerides, talc, titanium dioxide and carnauba wax.

³ PRILOSEC® (Astra Pharmaceuticals, L.P.), approved for the short-term treatment of erosive esophagitis (20 mg once a day for 4 to 8 weeks), short-term treatment of symptomatic GERD (20 mg once a day 4 to 8 weeks), maintenance of healing of erosive esophagitis (20 mg daily for up to 12 months), short-term treatment of active duodenal ulcer (20 mg once daily for up to 8 weeks), reduction of the risk of duodenal ulcer recurrence (40 mg once a day in combination with Clarithromycin 500 mg t.i.d.), short-term treatment of active benign gastric ulcer (40 mg once a day for 4-8 weeks) and long-term treatment of hypersecretory conditions [including Zollinger-Ellison syndrome (at individualized doses that start at 60 mg once a day)].

⁴ PREVACID® (TAP Pharmaceuticals, Inc.), approved for the short-term treatment of erosive esophagitis, maintenance of healing of erosive esophagitis, short-term treatment of active DU, short-term treatment of active benign GU, and the treatment of pathological hypersecretory conditions, including Z-E syndrome.

⁵ PANTO is a PPI intended for administration in GERD patients. The injectable formulation is intended for administration in GERD patients unable to take the oral dosage form.

of the Integrated Summary of Safety, submitted as part of the original NDA and a review of the Safety Update Report, submitted on October 21, 1998. Both reviews are provided as separate documents (Hugo E. Gallo-Torres, M.D., Ph.D., December 22, 1998).

TABLE 1
NDA 20-973: Reviewers

Indications ^a	MO Reviewer
1. Healing of erosive or ulcerative gastroesophageal reflux disease (GERD) (20 mg once daily, for up to 8 weeks)	Dr. J. Senior (November 30, 1998)
Long-term maintenance of healing of erosive or ulcerative GERD (20 mg or 10 mg, once daily; length of time not specified)	Dr. J. Senior (November 30, 1998)
2. Healing of duodenal ulcers (20 mg once daily for 4 weeks)	Dr. R. Prizont (December 4, 1998)
3. Treatment of pathological hypersecretory conditions including Zollinger-Ellison syndrome (long-term; doses starting at 60 mg once a day and adjusted to individual patient needs)	Dr. R. Prizont (December 4, 1998)
	Dr. H. Gallo-Torres (November 30, 1998)
Additional Reviews	
<ul style="list-style-type: none"> • Statistics (all indications) <ul style="list-style-type: none"> - Duodenal Ulcer - Healing of GERD - GERD Maintenance - Healing of Duodenal Ulcer 	Dr. M. Fan (October 26, 1998) (October 26, 1998) (November 9, 1998) (October 26, 1998) (October 26, 1998)
<ul style="list-style-type: none"> • Statistics (Expiry-dating) 	Dr. A.J. Sankoh (October 28, 1998)
<ul style="list-style-type: none"> • Pharmacokinetics/Pharmacodynamics 	Dr. C. Cronenberger (December 21, 1998)
<ul style="list-style-type: none"> • Pharmacology/Toxicology <ul style="list-style-type: none"> - Comments on Pharmacology/Toxicology Review of NDA 20-973 	Dr. Ke Zhang (December 18, 1998) Dr. J. Senior (December 18, 1998)
<ul style="list-style-type: none"> • Chemistry 	Dr. M. Kowblansky (December 2, 1998)
<ul style="list-style-type: none"> • Integrated Summary of Effectiveness 	Dr. H. Gallo-Torres (This memorandum)
<ul style="list-style-type: none"> • Integrated Summary of Safety 	Dr. H. Gallo-Torres (December 22, 1998)
<ul style="list-style-type: none"> • Review of October 21, 1998 Safety Update 	Dr. H. Gallo-Torres (December 22, 1998)
a) Indications 1. and 2. are addressed in one review (November 30, 1998) by Dr. J. Senior. Indications 3. and 4. are addressed in one review (December 4, 1998) by Dr. R. Prizont.	

III. RECOMMENDATIONS FOR REGULATORY ACTION: JUSTIFICATION, SUMMARY REVIEW OF THE EVIDENCE AND ADDITIONAL COMMENTS

A. Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

It is recommended that approval be granted for a regimen of 20 mg/day of RABE for 4 to 8 weeks for healing erosions/ulcerations of the esophagus associated with GERD. Reduction in symptoms of heartburn frequency, and the severity of daytime and nighttime heartburn have also been demonstrated. Superiority over ranitidine 150 mg q.i.d. for healing may be claimed.

It is recommended not to approve the requested claim of equivalence of RABE 20 mg/day to omeprazole 20 mg/day because of serious concerns and questions about the validity of the data from European studies. It is suggested that a confirming study be designed and carried out to do this. These recommendations are based on results of the following studies, evaluated in Dr. Senior's Medical Review.

Three studies have been done and reports submitted for the healing of erosive esophagitis associated with GERD indication: two North American trials (-NNRI and -NRRJ) and one European (-NRRP). These three healing studies had the same basic design, and the three protocols were almost identical. The study population (inclusion criteria and reasons for exclusion) was adequate for this type of study and consisted of patients with at least 3 months of GERD symptoms and esophageal lesions of severity/extent of grade 2 to 4. Neither patients with grade 0-1 (no erosive esophagitis) or 5 (strictures) were eligible. Mylanta antacid tablets were dispensed for symptomatic relief if needed, the use to be recorded. The primary measure of treatment success was the endoscopically-proven healing of the esophagitis to grade 0 or 1. Results of patients healed at 4 weeks who may have discontinued treatment were interpreted as showing healing at 8 weeks also. Results of secondary measures of effectiveness of treatment are not addressed in the present memorandum, but are described in detail in the MO's review. [Also noted in that review is the slower healing of more severe and extensive esophageal lesions and the fact that the optimal dose of rabeprazole for healing erosive esophagitis was not established.]

Dose-ranging study -NRRJ was a double-blind, randomized, 4-arm trial comparing healing effects of three dose levels of RABE (10, 20 or 40 mg/day) to placebo, administered for 4 or 8 weeks. The study was sized on the assumption of therapeutic gain of 43% (RABE=71%, PL=28%) in healing at 8 weeks, with 25 patients per arm (100 patients in total).

In study -NRRJ, a total of 20 participating investigators randomized 103 patients. The four randomized groups were comparable to each other in demographic and baseline disease characteristics, including endoscopy data.

Because results of planned statistical analyses (ITT and ENDO) were very similar, only ITT analysis data are presented here (Table 2). Significantly more ($p < 0.001$) patients were healed by any of the three RABE doses than by PL at both 4 and 8 weeks. At 8 weeks, the therapeutic gain with the 20 mg dose of RABE was 72% (higher than the projected 43%) and with the 10 mg

dose was 81%. There was no further benefit when the RABE dose was increased to 40 mg/day (therapeutic gain=73%).

NOTE: Because this reviewer's emphasis is on therapeutic gains, the efficacy Tables presented herein were taken from Dr. Fan's Statistical Review but the conclusions drawn from Dr. Senior's MO's review are the same.

TABLE 2
Study -NRRI

Summary Results of GERD Healing Rates
ITT Analysis^a

Treatment Group (mg)	Healing Rate	Therapeutic Gain (RABE-PL)	p-value ^b vs PL
I. Healing Rates at Week 4			
10	17/27 (63%)	63%	<0.001
20	14/25 (56%)	56%	<0.001
40	14/26 (54%)	54%	<0.001
PL	0/25 (0%)		
II. Healing Rates at Week 8			
10	25/27 (93%)	81%	<0.001
20	21/25 (84%)	72%	<0.001
40	22/26 (85%)	73%	<0.001
PL	3/25 (12%)		
<p>a) This analysis considers a missing endoscopy report as the same as the most recent non-missing result, that "allows all randomized patients to be analyzed, and treats missing values as treatment failures unless the patient has already healed at a previous visit"...</p> <p>b) Pairwise treatment p-value is adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-square statistics.</p>			
Data in this Table are the same as in sponsor's Table NRRI.6.2, Vol. 176, page 55.			

Results of study -NRRI are supported by those of study -NRRJ, a multicenter double-blind trial in 310 erosive esophagitis adults, comparing the healing effects RABE 20 mg/day to those of ranitidine, at the approved dose of 150 mg q.i.d. The criteria for patient selection, measures of efficacy and other aspects of study -NRRJ were the same as had been used in Study -NRRI. Sixty-three investigators randomized 338 patients, 169 to each study arm. The study was sized,

on the assumption of a therapeutic gain of 16% (expected healing rate with RABE 20 mg/day was 70%). By these estimates, 155 patients per arm would be needed.

The randomization process resulted in two treatment groups that were comparable to each other in demographic and baseline disease characteristics, including endoscopy data.

Both types of statistical analysis (ITT and ENDO) demonstrated superiority of RABE 20 mg/day to ranitidine 150 mg q.i.d. in the healing of erosions at both 4 weeks and for the combined healing at 8 weeks ($p < 0.001$ for all comparisons) (Table 3). These results, showing a therapeutic gain of 21% at 8 weeks (higher than the projected 13%), were very compelling in favor of the superiority of RABE 20 mg each morning over the standard approved regimen of RAN 150 mg four times a day, for the healing of endoscopic lesions of erosive esophagitis associated with GERD.

TABLE 3
Study -NRRJ

Summary Results of GERD Healing Rates
ITT Analysis^a

Proportions of Patients Healed		Therapeutic Gain	p-value ^b
RABE (20 mg/day)	RAN (150 mg q.i.d.)	(RABE-RAN)	
Healing Rates at Week 4			
98/167 (59%)	60/169 (36%)	23%	<0.001
Healing Rates at Week 8			
146/167 (87%)	112/169 (66%)	21%	<0.001
a, b) as per footnote to Table 2			

In addition to results of North American studies -NRRI and -NRRJ, the sponsor submitted results of a European study, -NRRP, comparing the healing rates of RABE 20 mg/day to omeprazole, 20 mg/day in 202 erosive esophagitis patients enrolled by 27 investigators. However, the MO's review has disclosed a number of irregularities in the study execution, which may invalidate the results. Consequently, in light of the irregularities of the European trial, approval of the claim for equivalence to omeprazole will be deferred.

The three randomized studies reviewed by the MO showed that RABE was, all in all, safe and well-tolerated. In study -NRRI there were no deaths reported; the serious adverse events were not likely to have been caused by test medication. Other AEs that did not cause serious effects or discontinuations were reported. Discontinuations were seen in all four study groups. Safety problems were not prominent in study -NRRJ and the 3 serious events occurring on RABE (and 2 on RAN) were not likely to have been caused by test medication. However, in this study, transient ALT elevations were seen in 7 patients during RABE administration, none to as much as twice the ULN, and in 1 on RAN. But no jaundice or other indications of liver effects were reported. ALT elevations will require further attention, particularly in the longer-term

maintenance trials. Study -NRRP showed that RABE 20 mg/day was safe and similarly well-tolerated as omeprazole 20 mg/day.

B. Maintenance of Healing of Erosive or Ulcerative Gastroesophageal Reflux Disease (GERD)

It is recommended that approval be granted for maintenance of healing and reducing the relapse rate of erosions/ulcerations in patients with already healed lesions of erosive esophagitis associated with chronic GERD, and for reduction in relapse rates of heartburn symptoms in these patients, at a daily dose of RABE 20 mg for a year.

Concerns for long-term use of RABE in non-pathological conditions are mentioned by Dr. J. Choudary in Dr. Zhang's Pharmacology/Toxicology review of December 18, 1998. These concerns, noted in Dr. Senior's memorandum of the same date, apply equally to the long-term use of the two previously-approved PPIs, omeprazole and lansoprazole; these have been administered to millions of patients for periods longer than 5 years. The pre-clinical findings of tumorigenicity/mutagenicity are of less concern because of the human experience accumulated so far. Nonetheless, we recommend continuation of the follow-up gastric biopsy program in those GERD maintenance patients administered RABE for up to 5 years, as well as post-marketing surveillance.

It is recommended not to approve the requested claim of equivalence of RABE 20 mg/day to omeprazole 20 mg/day because of serious concerns and questions about the validity of the data from European studies P (acute healing) and Q (maintenance of healing). It is suggested that a confirmatory study be designed and carried out to do this.

The recommendations for approval of the sought indication are based on results of the following studies, evaluated in Dr. Senior's Medical Review. Three studies have been done and reports submitted for the maintenance of healing indication. These included two North American trials (-NRRK-odd and -NRRK-even) intended to demonstrate superiority of RABE 10 or 20 mg/day over PL in maintaining the endoscopically proven healing of erosive esophagitis, assuming that RABE would reduce the relapse rate within a year by at least 24%. An active comparator European study (-NRRQ) was set to show the bioequivalence of RABE 20 mg/day to omeprazole 20 mg/day in maintaining healing of the erosive esophagitis associated with GERD, assuming a relapse rate of 20% for both agents.

The original protocol for the PL-comparison study had called for enrollment of 240 adults with healed erosive esophagitis. An amendment to the protocol before initiation of the trial doubled the number of patients to 480, and split the study into K-odd (RABE, 10 mg, n=70; RABE 20 mg, n=69; PL, n=70; for a total of 209 patients) and K-even (RABE, 10 mg, n=95; RABE, 20 mg, n=94; PL, n=99; for a total of 288 patients). Both trials (K-odd and K-even) were well-designed and apparently well-executed. Healing may have occurred either in study -NRRJ (no repeat endoscopy needed if randomization into study K-odd or even occurred within 7 days) or under "standard clinical care within 90 days but with endoscopic confirmation, before randomization". Healing was adequately defined as a decrease in grade lesions from 2, 3 or 4 grade to grade 0 or 1. The treatment duration was 52 weeks. Follow-up visits with endoscopy

were scheduled at 4, 13, 26 and 52 weeks, and a visit without endoscopy at 39 weeks. Finding of grade 2 esophagitis or worse was to be interpreted as showing relapse of disease. As pointed out by the MO, of the 209 patients that were randomized into the maintenance study -NRRK-odd, almost half (101/209, 48.3%) did not complete the full study, mostly because of relapse in 53 (25.4%) or lack of perceived efficacy by 12 (5.7%) patients, significantly more ($p < 0.001$) in the PL group. Similarly, of the 243 patients that were randomized into the maintenance study, -NRRK-even, almost half (135/288, 46.9%) did not complete the full 52 weeks of the study, mainly because of relapse or because of a lack of perceived efficacy by 96 (33.3%) patients, significantly more ($p < 0.001$) in the PL group. In both trials, the three randomized groups were comparable to each other in demographic and baseline disease characteristics, which included endoscopy data.

The results of study -NRRK-odd showed highly significant ($p < 0.001$) and clinically impressive reductions in the relapse rate on either dose of RABE throughout the study, especially on 20 mg/day. In addition to being shown superior to PL, this RABE dose was also shown superior to the 10 mg/day dose. At the end of 52 weeks, only 7 of the 67 (10.4%) patients who had received RABE 20 mg had relapsed, compared to 18/66 (27.3%) on RABE 10 mg/day ($p = 0.027$). It is not necessary to resort to statistical analyses with results such as those displayed in the Figure on page 63 of the MOR. Although the 10-mg dose was very effective for prevention of relapse, the 20-mg dose of RABE was even more effective.

The results of study -NRRK-odd were supported by those of study -NRRK-even, as shown in the Figure on page 79 of the MO's review. Superiority of both doses of RABE was highly significant, with very impressive reductions in the relapse rate compared to PL. However, the difference was not significant for RABE 20 mg/day when compared to RABE 10 mg/day, at any point throughout the trial and at the end of 52 weeks.

A third study (-NRRQ) was set to demonstrate the equivalence of two dose levels of RABE (10 or 20 mg/day) to omeprazole 20 mg/day. However, the results of this study cannot be used to demonstrate equivalence between the PPIs because of the questions raised by the MO about this trial as well as for Study P (short-term healing) which preceded it. In addition, Study Q showed unexplained major differences in relapse rate for patients who were treated with RABE, compared to those treated with omeprazole. Further data are needed before the claim of equivalence for this indication can be considered.

Some safety problems were reported in the three 12-month maintenance studies. However, when comparisons to PL are considered, it is important to note that patients in this group were under observation for significantly ($p < 0.001$) shorter times than either RABE groups. In addition - as a consequence of more dropouts for relapses - there was a significantly ($p < 0.009$) shorter period of observation for the RABE 10-mg/day group when compared to the 20-mg/day group. There were no deaths reported during Study -NRRK-odd; the serious adverse events, all requiring hospitalization, were not related to RABE or PL. Most arose from previous medical problems pre-dating randomization of the patients into the trial or were simply intercurrent events that would be expected in such a population sample. Treatment-emergent symptoms that occurred in significantly higher frequency in the RABE-treated patients than in those treated with PL included unspecified pain, diarrhea and specified infections. Three patients died after study

-NRRK-even, but none of these deaths or the serious adverse events occurring in this trial appeared related to test medication. Similarly, when exposure time is considered, none of the other treatment-emergent AEs occurred significantly more frequently in the RABE-treated group than in the one treated with PL. Study -NRRQ did not show marked differences in the AE profile of RABE compared to omeprazole. The MO noted three cases of M.I. in the patients on RABE 20 mg/day, compared to none in either of the groups that were taking omeprazole 20 mg/day or RABE 10 mg/day. Although notable, this difference was not significant ($p=0.11$). The issue of rabeprazole and adverse events related to the cardiovascular system is addressed in detail in Dr. Gallo-Torres' reviews of the ISS (December 22, 1998) and the October 21, 1998 SU Report (December 22, 1998.)

C. Healing of Duodenal Ulcers

It is recommended that approval be granted for the treatment of active duodenal ulcer, at the oral dose of 20 mg, after the morning breakfast, for a period not shorter than 4 weeks. Symptomatic relief has also been demonstrated. Equivalence to omeprazole 20 mg Q AM may be claimed.

It is recommended not to grant a claim of either superiority or equivalence to ranitidine 150 mg BID. These recommendations are based on results of three pivotal multicenter trials, evaluated in Dr. Prizont's Medical Officer's Review.

Results of three pivotal, controlled clinical trials were submitted by the sponsor in support of the claim of effectiveness of RABE in the treatment of active duodenal ulcer: -NRRC (USA), comparing RABE 20 mg QAM and 40 mg QAM to PL; -NRRL (Europe), comparing RABE 20 mg QAM to omeprazole, 20 mg QAM; and -NRRD (USA), set to demonstrate superiority of RABE 20 mg QAM to RAN 150 mg BID. The trials used - all in all - similar study design and were apparently well-executed. The study population was adequate for the proposed duodenal ulcer indication. The primary efficacy endpoint was the complete healing of duodenal ulcer, proven endoscopically, at 0, 2 and 4 weeks. Patients healed at 2 weeks were not required to return for the week 4 endoscopy. Acetaminophen was allowed for the relief of pain. Although Mylanta® was provided, the patients were not discontinued if they took this antacid during the trials. Other aspects of the trials were also adequate.

In study -NRRC, 21 USA investigators randomized a total of 100 DU patients [PL, n=33; RABE 20 mg/day, n=34; RABE 40 mg/day n=33] that were treated with test medication for 4 weeks. The randomization process accomplished three treatment groups that were comparable to each other in number of DU patients, demographic and disease characteristics, including endoscopy data.

Because results of planned statistical analyses (ITT and ENDO) were similar, only ITT data are presented here (Table 4). After the first 2 weeks of therapy, the proportion of DU patients healed with either dose of RABE did not significantly differ from PL. Significantly more ($p<0.001$) patients were healed by either of the two RABE doses than by PL at 4 weeks. At this time, the therapeutic gain with the 20-mg dose of RABE was 40% (somewhat higher than the projected 36%) and with the 40 mg dose was 52%. This study showed that there was no further benefit

when the RABE dose was increased from 20 to 40 mg/day since, although numerically different, the effects of these doses of the drug were not statistically different from one another.

TABLE 4
Study -NRRC

Summary Results of Duodenal Ulcer Healing Rates^a
ITT Analysis

Treatment Group (mg)	Healing Rate	Therapeutic Gain (RABE-PL)	p-value ^b		
			PL vs RABE (mg/day)		RABE (mg)
			20	40	20 vs 40
I. Healing Rates at Week 2					
20	15/34 (44%)	23%	N.S.		N.S.
40	14/33 (42%)	21%	N.S.		
PL	7/33 (21%)				
II. Healing Rates at Week 4					
20	27/34 (79%)	40%	0.001		N.S.
40	30/33 (91%)	52%	<0.001		
PL	13/33 (39%)				
<p>a) Pairwise treatment p-value was adjusted for investigator; obtained using stratified Mantel-Haenszel Chi-square statistic.</p> <p>b) <u>Healed</u>: Complete regeneration of the mucosa (re-epithelialization) with no visible ulcer craters.</p>					

Results of study -NRRC are supported by those of study -NRRL, a trial designed to demonstrate comparability between RABE 20 mg and omeprazole 20 mg QAM. The 25 European investigators in 9 European countries randomized a total of 205 patients, of which 102 were assigned to RABE and 103 to omeprazole. The randomization process accomplished two treatment groups that were comparable to each other in all important baseline characteristics, including number of patients with DU, other demographic and disease characteristics, and endoscopy data. As depicted in Table 5, the RABE and omeprazole treatment groups had comparable 2- and 4-week healing rates.

TABLE 5
Study -NRRL

Summary Results of Duodenal Ulcer Healing Rates^a
ITT Analysis

Treatment Group (mg)	Healing Rate	Therapeutic Gain (RABE-OME)	p-value ^a Rabe vs OME
I. Healing Rates at Week 2			
RABE 20	70/102 (69%)	8%	N.S.
OME 20	63/103 (61%)		
II. Healing Rates at Week 4			
RABE 20	100/102 (98%)	5%	N.S.
OME 20	96/103 (93%)		
a, b) As in footnote to Table 4			

According to the observations in Dr. Prizont's review of results of USA study -NRRL, the sponsor's claim of superior RABE 20 mg QAM efficacy to ranitidine 150 mg BID was not substantiated and was apparently skewed by one center (Inv. #10). In this center, all of the 13 patients randomized to RABE and all 13 randomized to ranitidine, were unhealed after 2 weeks of treatment. An additional 2 weeks of therapy was associated with a rather anomalous result since 12/13 of the RABE patients (92%) had healed but only 7/13 (54%) of those given ranitidine had healed. Hence, this large center had an overall 73% healing gain in 2 weeks of therapy. The reasons for these results are unclear. The MO hypothesizes that - at this center - all ulcers treated with RABE were decreasing rapidly in size and were already very small at the time of the week 2 endoscopy. Knowledge of ulcer size at week 2 endoscopy was, therefore, important but this information was not provided by the sponsor. Based on all of these considerations, it is recommended that **no claim of either superiority or equivalence to ranitidine 150 mg BID be granted.**

D. Treatment of Pathological Hypersecretory Conditions, Including Zollinger-Ellison Syndrome

It is recommended that approval be granted for the use of RABE for the treatment of gastric acid hypersecretion including Zollinger-Ellison syndrome. The recommended adult oral dose varies with the individual patient but should start with 60 mg once a day.