

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-456

20-973/S-013

MICROBIOLOGY REVIEW

MICROBIOLOGY REVIEW
DIVISION OF SPECIAL PATHOGEN AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDA #: #21-456

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SUBMISSION REVIEWED: Original NDA for *H. pylori* eradication

DRUG CATEGORY: Proton pump inhibitor

INDICATIONS: This application: *Helicobacter pylori* Eradication in Patients

DOSAGE FORM: Delayed-Release enteric-coated Tablets—20 mg/tablet

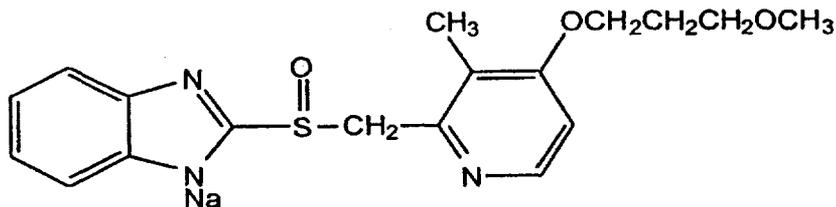
DRUG PRODUCT NAME

PROPRIETARY: ACIPHEX®

NONPROPRIETARY/USAN: Rabeprazole sodium

CHEMICAL NAME: 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*-benzimidazole sodium salt

STRUCTURAL FORMULA:



Molecular Formula: C₁₈H₂₀N₃NaO₃S

Molecular Weight: 381.42

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ACIPHEX® (rabeprazole sodium) for *H. pylori*

SUPPORTING DOCUMENTS: IND ——— —rabeprazole sodium for eradication of *Helicobacter pylori* in *Helicobacter pylori* infected patients.

REMARKS/COMMENTS:

This is an original New Drug Application for ACIPHEX® (rabeprazole sodium) 20 mg Delayed-Release tablets in combination with antibiotics (clarithromycin and amoxicillin) for the eradication of *Helicobacter pylori* in patients with duodenal ulcer disease or a history of duodenal ulcer disease.

CONCLUSIONS:

1. About 9% of the *Helicobacter pylori* isolates in the clinical trial 604 (the only trial which used NCCLS methods) were resistant (MIC ≥ 1 $\mu\text{g/mL}$) to clarithromycin pre-treatment. The distribution of pre-treatment clarithromycin MIC values was bimodal. One population had MIC values of ≤ 0.125 $\mu\text{g/mL}$ and the other population had MIC values of ≥ 8 $\mu\text{g/mL}$. A few isolates had MIC values between these two populations. Patients with isolates that had high clarithromycin MICs did not have their *Helicobacter pylori* eradicated as readily as those with isolates with low clarithromycin MIC values. All but two *H. pylori* isolates in this clinical trial were susceptible (MIC ≤ 0.25 $\mu\text{g/mL}$) to amoxicillin. Eradication rates did not seem to be related to amoxicillin MIC values.
2. Treatment with rabeprazole plus amoxicillin and clarithromycin (RAC) for 3-days resulted in a low *Helicobacter pylori* eradication rate of 27%. Treatment with RAC for 7-days (77% eradication rate in the ITT population) and RAC for 10-days (78% eradication rate) gave results similar to those obtained with omeprazole plus amoxicillin and clarithromycin (OAC) after 10-days of treatment (73% eradication rate).
3. Treatment with RAC or OAC did not lead to an increase in resistance to clarithromycin. All post-treatment isolates were susceptible to amoxicillin.

RECOMMENDATIONS:

The application is approvable from the microbiological viewpoint under section 505(b) of the Act. Minor changes should be made to the microbiology subsection of the label. The revised Microbiology section of the labeling is attached on pages 57-59 of this review.

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ACIPHEX® (rabeprazole sodium) for *H. pylori*

EXECUTIVE SUMMARY

The sponsor is seeking approval of rabeprazole sodium in combination with clarithromycin and amoxicillin for the eradication of *Helicobacter pylori* in infected patients with duodenal ulcer disease or a history of duodenal ulcer disease. The product is also known as E3810 and LY307640.

Rabeprazole is a substituted benzimidazole proton-pump inhibitor. This class of compounds suppresses gastric acid secretion by inhibiting the gastric H⁺, K⁺ ATP-ase at the secretory surface of the gastric parietal cell. Although rabeprazole has been shown to inhibit the proliferation of *Helicobacter pylori* *in vitro*, studies have failed to elucidate the mechanism by which this activity is manifested.

Rabeprazole was found to bind to the sulfhydryl (SH) group in *Helicobacter pylori* urease active sites and inactivate the enzyme. The thioether of rabeprazole was inactive against urease.

When the activity of rabeprazole on the growth of *H. pylori* was compared to its ability to inhibit several enzyme systems, the drug's inhibition of adenine incorporation into RNA was within the same concentration range as that which inhibits growth. It has been speculated that this inhibition may play some role in the antibacterial activity of rabeprazole against *Helicobacter pylori*.

Although it is not clear how rabeprazole enhances the effect of antibiotics it has been postulated that rabeprazole may either enhance the activity of the antibiotics by increasing the pH of the environment or by making the organism more vulnerable to the antibiotics by decreasing acid output.

The antibacterial activity of rabeprazole and its thioether metabolite were evaluated *in vitro* against *Helicobacter pylori*. Activity was compared to other agents by the agar dilution method. Results are shown in TABLE A.

TABLE A
Activities of Proton Pump Inhibitors, Their Metabolites, and Antibiotics
Against 15 Strains of *Helicobacter pylori*

Compound	Range	MIC (µg/mL)	
		MIC ₅₀	MIC ₉₀
Rabeprazole sodium		1.56	3.13
Rabeprazole thioether		1.56	1.56
Omeprazole		25	50
Omeprazole thioether		12.5	25
Lansoprazole thioether		12.5	25
Roxithromycin		0.2	50
Aminobenzyl penicillin		0.10	0.39
Ofloxacin		0.78	3.13

The above data demonstrate that rabeprazole and its thioether metabolite both have activity against *H. pylori* that is only slightly less than that of ofloxacin. Omeprazole and lansoprazole showed only slight activity against *H. pylori*.

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A study was performed in gerbils to determine the effect of rabeprazole with clarithromycin and amoxicillin on the eradication of *H. pylori* from the stomach of experimentally infected animals. Results are summarized in TABLE B.

TABLE B
Effect of Rabeprazole and Antibiotics Alone Or in Combination
on *H. pylori* Eradication from Gerbil Gastric Mucosa

Treatment	Number of Viable Cells (Log CFU/g of tissue)
Control	6.2
Rabeprazole Alone	6.2
Amoxicillin plus Clarithromycin	4.4
Rabeprazole plus Amoxicillin and Clarithromycin	2.1

These data demonstrate that rabeprazole alone was no better than placebo in eradicating *Helicobacter pylori* from gerbil stomachs. Treatment with amoxicillin plus clarithromycin produced about a 100-fold reduction in the number of viable cells of *H. pylori* in the gastric/mucosa of gerbils as compared to untreated controls. When therapy was augmented with rabeprazole the bacterial count was 10,000-fold less than those in controls, or a 100-fold greater reduction than produced in the group treated with amoxicillin plus clarithromycin without rabeprazole.

Three clinical trials were performed to determine the efficacy and safety of rabeprazole, amoxicillin, clarithromycin triple therapy for eradication of *H. pylori*.

1. E3810-E044-602--A Pilot Study to Compare the Efficacy and Safety Profile of Four Treatment Regimens for the Eradication of *Helicobacter pylori* Patients with Chronic Antral Gastritis or Peptic Ulcer Disease.
2. E3810-E0440-603--A Multi-Center Study to Compare the Efficacy and Safety Profile of Two Rabeprazole and Two Omeprazole Triple Therapy Regimens Administered For 7 Days for the Eradication of *Helicobacter pylori* in Subjects with Documented Peptic Ulcer Disease and *Helicobacter pylori* Infection.
3. E3810-A001-604--Comparison of the Efficacy and Safety of Three Rabeprazole-based Triple Therapy Regimens to Omeprazole-based Triple Therapy for Eradication of *Helicobacter pylori*.

Study 602 was a single center pilot study conducted in Europe to determine the eradication potential of rabeprazole triple therapy and dual therapy. Patients had an endoscopy at which biopsies for *H. pylori* status was performed pre-treatment. Patients were randomized to receive one of the following four treatments for 7 days (1) rabeprazole + amoxicillin + clarithromycin (RAC), (2) rabeprazole + amoxicillin + metronidazole (RAM), (3) rabeprazole + clarithromycin + metronidazole (RCM), or (4) rabeprazole + clarithromycin (RC). Efficacy was based on the presence or absence of *H. pylori* post-treatment. ¹³C-UBT (urea breath test) was performed 5 and 9 weeks after the start of treatment. Patients with a positive ¹³C-UBT at either follow-up visit underwent another endoscopy at which biopsies were taken for *H. pylori* status. TABLE C shows the results of this study. From this table it can be seen that dual therapy is not as efficacious as triple therapy.

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TABLE C
Eradication Rates for *Helicobacter pylori* (Study-602)

Treatment	Intent-to-Treat		Per-Protocol	
	No. Patients	% Patients	No. Patients	% Patients
RAC	18/19	94.7	18/18	100.0
RAM	17/19	89.5	15/17	88.2
RCM	18/18	100.0	17/17	100.0
RC	12/19	63.2	12/18	66.7
Overall	65/75	86.7	62/70	88.6

Susceptibility to amoxicillin, metronidazole, and clarithromycin was determined by E-test. Breakpoints used were as follows; amoxicillin susceptible, MIC ≤ 0.25 $\mu\text{g/mL}$, resistant MIC > 0.25 $\mu\text{g/mL}$; clarithromycin susceptible, MIC ≤ 0.1 $\mu\text{g/mL}$, resistant MIC > 0.1 $\mu\text{g/mL}$; metronidazole susceptible, MIC ≤ 8 $\mu\text{g/mL}$, resistant > 8 $\mu\text{g/mL}$. Initially the antral biopsies were cultured. Corpus biopsies were only cultured if the antral cultures were negative. To be considered evaluable a patient had to be *H. pylori* positive on histopathology and/or culture. The E-test is not an approved NCCLS susceptibility test method for *H. pylori*. The breakpoints used for clarithromycin are also not the approved NCCLS breakpoints of susceptible ≤ 0.25 $\mu\text{g/mL}$, intermediate 0.5 $\mu\text{g/mL}$, and resistant ≥ 1.0 $\mu\text{g/mL}$. All amoxicillin MIC were ≤ 0.064 $\mu\text{g/mL}$. The metronidazole MICs varied from 0.032 $\mu\text{g/mL}$ to ≥ 32 $\mu\text{g/mL}$. Many isolates with metronidazole MICs of ≥ 32 $\mu\text{g/mL}$ were eradicated. Almost all pre-treatment clarithromycin MICs were ≤ 0.38 $\mu\text{g/mL}$. After treatment failure, especially with rabeprazole and clarithromycin alone, MIC values increased to ≥ 0.5 $\mu\text{g/mL}$.

Study 603 compared rabeprazole and omeprazole triple therapy. Treatment was for seven days with a follow-up period of 12 weeks. Patients were randomized to receive one of four treatments (1) rabeprazole + amoxicillin + clarithromycin (RAC), (2) rabeprazole + clarithromycin + metronidazole (RCM), (3) omeprazole + amoxicillin + clarithromycin (OAC), or (4) omeprazole + clarithromycin + metronidazole (OCM). Successful eradication of *H. pylori* was defined as a negative ^{13}C -UBT (urea breath test) at both a week 5 and week 13 post-treatment assessment. TABLE D shows the results of this study. It appears that rabeprazole is equivalent to omeprazole when combined with amoxicillin and clarithromycin. Omeprazole may be better than rabeprazole when combined with clarithromycin and metronidazole.

TABLE D
Helicobacter pylori Eradication Rate For the ITT Population
(Study 603)

Treatment Group	ITT Population	PP Population
RAC	70/83 (84%)	61/65 (94%)
OAC	61/85 (72%)	53/63 (84%)
RCM	56/81 (69%)	48/61 (79%)
OCM	67/85 (79%)	57/66 (86%)

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Sensitivity testing was performed in this study by E-test methodology. The same criteria were used as in study 602. TABLE E shows the eradication rate based on sensitivity at the screening visit.

TABLE E
Eradication Rate by Antibiotic Sensitivity at Screening
Pre-Protocol Population (Study 603)

Micro Results	RAC N=65		OAC N=63		RCM N=61		OCM N=66	
	No. of Subjects	% Eradication						
Sens	55	95	57	88	50	80	61	85
Fully	52	94	54	93	39	79	44	91
Partial	3	100	3	0	11	82	17	71
C-sens	1	100	0	0	8	88	13	85
C-res	2	100	3	0	3	67	4	25
Resistant	0	0	0	0	1	0	0	0
Unknown	10	90	6	50	10	80	5	100
Total		94		84		79		86

Micro--Microbiology

Sens--Sensitive

Fully--sensitive to both antibiotics received

Partially—sensitive to one of the antibiotics received and resistant to the other

C-sens—sensitive only to clarithromycin and resistant to the other antibiotic

C-res—sensitive only to amoxicillin/metronidazole and resistant to clarithromycin

The number of subjects with isolates sensitive to one or more of the antibiotics was similar in each of the four treatment groups, as was the percentage eradication. In all groups the majority of subjects had isolates that were fully sensitive at screening. The metronidazole treatment groups had a lower percentage of subjects with fully sensitive isolates than did subjects in the amoxicillin treatment groups. There was a lower eradication rate in clarithromycin resistant isolates than for sensitive isolates. Sensitivity was unknown in a number of subjects.

All amoxicillin MICs, except one at 0.5 µg/mL, were ≤0.25 µg/mL. The metronidazole MICs varied from ≤0.016 µg/mL to ≥256µg/mL. Many isolates with MICs of ≥256 µg/mL were eradicated. Almost all pre-treatment clarithromycin MICs were ≤0.38 µg/mL. Isolates with clarithromycin MICs ≥0.25 µg/mL tended to be failures.

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Study 604 was a multi-center study designed to compare *H. pylori* eradication regimens in approximately 800 patients. Patients were randomized into one of the following four treatment groups: (1) rabeprazole + amoxicillin + clarithromycin for 3 days (RAC-3), (2) rabeprazole + amoxicillin + clarithromycin for 7 days (RAC-7), (3) rabeprazole + amoxicillin + clarithromycin for 10 days (RAC-10), or (4) omeprazole + amoxicillin + clarithromycin for 10 days (OAC-10). A ¹³C-UBT and endoscopy were performed pre-treatment. Susceptibility testing for clarithromycin and amoxicillin were performed using NCCLS methods. A post-treatment assessment was performed 6 to 10 weeks after treatment. All patients had a ¹³C-UBT at this assessment. If the ¹³C-UBT was positive, the patient underwent a follow-up endoscopy and biopsies were taken. TABLE F shows the eradication rates in this study.

TABLE F
Summary of *Helicobacter pylori* Outcome—ITT population
(Study 604)

Treatment	RAC N (%)		OAC N (%)	
	Eradicated	Not Eradicated	Eradicated	Not Eradicated
RAC 3-day vs OAC	51 (27%)	136 (73%)	151 (73%)	55 (27%)
RAC 7-day vs OAC	150 (77%)	44 (23%)	151 (73%)	55 (27%)
RAC 10-day vs OAC	153 (78%)	43 (22%)	151 (73%)	55 (27%)

The 3-day RAC treatment was not very successful in eradicating *H. pylori*. Both the 7-day and 10-day RAC treatments appear to be about equal in eradication rates and both seem to be very similar to the eradication rate seen with 10-day OAC treatment.

In this study 90.5% (507/560) of the isolates were susceptible (MIC ≤ 0.25 $\mu\text{g/mL}$), <1% (2/560) were intermediate (MIC = 0.5 $\mu\text{g/mL}$), and 9.1% (51/560) were resistant (MIC ≥ 1 $\mu\text{g/mL}$) to clarithromycin at baseline. There were only two isolates that were not susceptible to amoxicillin (MIC ≤ 0.25 $\mu\text{g/mL}$). These two isolates had amoxicillin MICs of 0.5 $\mu\text{g/mL}$. Only 9 of the 53 (17%) of the clarithromycin resistant isolates were eradicated. Approximately 80% of the clarithromycin sensitive isolates were eradicated in the RAC 7-day, RAC 10-day, and OAC 10-day treatment groups. Only about 27% were eradicated in the RAC 3-day treatment group. Treatment does not seem to increase clarithromycin MICs in *H. pylori* isolates that were not eradicated. Most amoxicillin MICs were ≤ 0.06 $\mu\text{g/mL}$. Eradication does not seem to be related to amoxicillin MIC values. One of the two isolates with an amoxicillin MIC of 0.5 $\mu\text{g/mL}$ was eradicated.

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PRECLINICAL EFFICACY (IN VITRO)

MECHANISM OF ACTION

Rabeprazole sodium

Rabeprazole is a substituted benzimidazole proton-pump inhibitor. This class of compounds does not exhibit anticholinergic or histamine H₂-receptor antagonist properties. These compounds suppress gastric acid secretion by inhibiting the gastric H⁺, K⁺ ATP-ase at the secretory surface of the gastric parietal cell. Because this enzyme is regarded as the acid (proton) pump within the parietal cell, rabeprazole has been characterized as a gastric proton pump inhibitor. Rabeprazole blocks the final step of gastric acid secretion. Through inhibition of the H⁺/K⁺ -ATPase in these cells, the drug decreases acid output.

Although rabeprazole has been shown to inhibit the proliferation of *Helicobacter pylori* *in vitro*, studies have failed to elucidate the mechanism by which this activity is manifested.

The effects of the thioether metabolite of rabeprazole sodium on the morphology of *Helicobacter pylori* NCTC 11916 was examined (1). Electron transmission microscopy was used to examine the effects of 1, 2, 4 and 8 times the MIC. The ribosomes of untreated bacteria were evenly distributed throughout the cytoplasm and the outer and inner membranes of the cell wall were clearly distinguishable. Bacteria treated with thioether concentrations of 1 times the MIC and higher had fingerprint-like structures that were not observed in control bacteria. The electron density of the space between the outer and inner membranes of the cell wall had also increased. At 4 times the MIC, scattered swollen cells were observed and the cytoplasmic material of the swollen cells was less dense. The thioether appears to exert its antibacterial effect against *H. pylori* by affecting the components of the cell wall.

Another study (2) examined the effects of the thioether metabolite of rabeprazole sodium on the morphology of *Helicobacter pylori* NCTC 11916 at concentrations of ½, 1, 2, 4, and 8 times the MIC. This study used scanning electron microscopy. Unlike study (1) that used transmission microscopy, this study showed no marked changes in bacteria even at 8 times the MIC.

The inhibitory effect of rabeprazole on *H. pylori* urease activity was examined (3). Rabeprazole sodium was found to bind to the sulfhydryl (SH) group in *Helicobacter pylori* urease active sites. The inhibitory effect of rabeprazole was influenced by the pH of the reaction mixture. At pH 5.0 against urease activity in intact cells, rabeprazole displayed an IC₅₀ of 0.24 μM. Values were 4.2 and 40 μM at pH 7.0 and 8.5, respectively. Rabeprazole displayed similar effects against cell-free urease; IC₅₀ values were 0.29, 7.6, and 55 μM at pH 5.0, 7.0, and 8.5, respectively. The thioether of rabeprazole was inactive at 1000 μM against cell-free urease at pH 5.0 and 8.5.

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Another study (4) evaluated the effects of rabeprazole on the growth of *H. pylori* and its inhibition of several enzyme systems. The results are shown in TABLE 1.

TABLE 1
Activity of Rabeprazole in a Variety of Enzyme Systems

Activity Tested in <i>Helicobacter pylori</i>	Rabeprazole IC ₅₀ Value μM
Growth Inhibition (Bacterial Count)	3
Pyruvate Induced ATP Synthesis	95
Proton Extrusion Value from Pyruvate Induced ATP Synthesis	16
ATPase in Bacterial Extract	>1000
ATPase in Intact Bacteria	220
Urease	20
Aspartic Acid Uptake in <i>H. pylori</i>	>100
Aspartic Acid Incorporation into <i>H. pylori</i>	14
Adenine Uptake into <i>H. pylori</i>	43
Adenine Total Incorporation into <i>H. pylori</i>	7.6
Adenine Incorporation in RNA	4.9
Adenine Incorporation in DNA	10

Since the inhibition of adenine incorporation into RNA (IC₅₀ = 4.9μM) is within the same concentration range as that which inhibits growth (3 μM), it has been speculated that this inhibition may play some role in the antibacterial activity of rabeprazole against *Helicobacter pylori*.

It is not clear how rabeprazole enhances the effect of antibiotics, but two theories have been proposed. *H. pylori* has evolved to live in an acid environment and seems to have a requirement for a small amount of acid. Rabeprazole decreases acid output and may render the organism more vulnerable to the effect of an antibiotic. Alternatively there are certain antibiotics such as amoxicillin and especially clarithromycin which are increasingly active as the pH increases. Rabeprazole suppresses acid production and may, therefore, enhance the activity of these antibiotics.

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ACIPHEX® (rabeprazole sodium) for *H. pylori***Amoxicillin**

Amoxicillin is a beta-lactam antibiotic. These drugs block the final stage in bacterial cell wall formation. Bacteria have a rigid, covalently linked framework surrounding them. This is a complex polysaccharide-peptide called a peptidoglycan. It consists of parallel polysaccharide chains cross-linked by short peptide chains. The basic recurring unit in the polysaccharide chains consists of a disaccharide of N-acetyl-D-glucosamine in β (1-6) linkage with N-acetylmuramic acid. To the hydroxyl group of the lactic acid substituent of muramic acid is attached a tetrapeptide side chain containing L-alanine, D-alanine, D-glutamic acid, and either diaminopimelic acid or L-lysine. The long parallel polysaccharide chains are cross-linked by their peptide side-chains. The terminal, D-alanine residue of the peptide side-chain of one polysaccharide chain is joined covalently with the peptide side-chain in an adjacent polysaccharide chain, either directly or through another short peptide. It is this cross-linking step that is blocked by beta-lactam antibiotics.

Clarithromycin

Clarithromycin exerts its antibacterial activity by inhibition of protein synthesis via high affinity binding to the bacterial ribosome. This binding involves interactions with the 23S rRNA and ribosomal proteins of the 50S ribosomal subunit at the peptidyl transfer site. These interactions prevent the bacterial cell from producing structural proteins and enzymes necessary for growth and multiplication.

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ACIPHEX® (rabeprazole sodium) for *H. pylori***ACTIVITY AGAINST *H. PYLORI*****Rabeprazole**

The antibacterial activity of rabeprazole sodium and its thioether metabolite were evaluated *in vitro* against *Helicobacter pylori* (5). Activity was compared to that of omeprazole, omeprazole-thioether, lansoprazole-thioether, roxithromycin, aminobenzyl penicillin and ofloxacin. MICs were determined by the agar dilution method. Brucella Agar supplemented with 7% defibrinated horse blood was used. Incubation was at 37°C for three days in an atmosphere containing 10% CO₂. The bacterial inoculum contained approximately 5 x 10⁵ CFU/spot. The results are shown in TABLE 2.

Rabeprazole sodium and its thioether metabolite showed no antibiotic activity against other Gram-positive (*Staphylococcus aureus*, *Enterococcus faecalis*) and Gram-negative (*Escherichia coli*, *Klebsiella pneumoniae*, *Citrobacter freundii*, *Enterobacter cloacae*, *Serratia marcescens*, *Proteus* species, and *Pseudomonas aeruginosa*) bacteria at concentrations as high as 100 µg/mL.

TABLE 2
Activities of Proton Pump Inhibitors, Their Metabolites, and Antibiotics
Against 15 Strains of *Helicobacter pylori*

Compound	MIC (µg/mL)		
	Range	MIC ₅₀	MIC ₉₀
Rabeprazole sodium		1.56	3.13
Rabeprazole thioether		1.56	1.56
Omeprazole	—	25	50
Omeprazole thioether	—	12.5	25
Lansoprazole thioether	—	12.5	25
Roxithromycin	—	0.2	50
Aminobenzyl penicillin	—	0.10	0.39
Ofloxacin		0.78	3.13

The above data demonstrate that rabeprazole and its thioether metabolite both have activity against *H. pylori* that is only slightly less than that of ofloxacin. Omeprazole and lansoprazole showed only slight activity against *H. pylori*.

The checkerboard titration method was employed to examine the antimicrobial effect of the combinations of rabeprazole sodium and amoxicillin, rabeprazole sodium and clarithromycin, and amoxicillin and clarithromycin with media adjusted to pH 5.5 and pH 7.1 (6). Twenty-seven strains of *Helicobacter pylori* were tested. The strains included 26 clinical isolates and the NCCLS-approved quality control strain *H. pylori* ATCC 43504. The test media was Mueller-Hinton Agar fortified with 5% defibrinated sheep blood. Incubation was at 35°C for 3 days in a microaerobic atmosphere. The combinations were assessed by evaluating the MICs provided by each agent alone in comparison with the MIC of each drug in combination. The Σ FIC Index (Fractional Inhibitory Concentration index) is utilized to mathematically express the interaction of two antibacterial agents. The Σ FIC Index was calculated by using the MIC values

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obtained from comparing each agent alone and in combination. The \sum FIC Index was obtained from the following formula:

$$\sum \text{FIC Index} = \frac{(\text{MIC of Drug \#1 in combination} / \text{MIC of Drug \#1 alone})}{(\text{MIC of Drug \#2 in combination} / \text{MIC of Drug \#2 alone})}$$

The mutual effects between the agents by the \sum FIC Index are defined as follows:

Synergistic Effect	$\sum \text{FIC} \leq 0.5$
Additive Effect	$\sum \text{FIC} > 0.5 \text{ to } \leq 1$
Indifference	$\sum \text{FIC} > 1 \text{ to } \leq 2$
Antagonistic Effect	$\sum \text{FIC} > 2$

TABLE 3 shows the result of the combination effect of rabeprazole sodium and the antimicrobial agents amoxicillin and clarithromycin. TABLE 4 shows the result of the combination effect of amoxicillin and clarithromycin.

TABLE 3
The Combination Effects of Rabeprazole Sodium and Antimicrobial Agents
On *Helicobacter pylori*

PH of Medium	Antimicrobial Drugs	Number of Strains	Range of \sum FIC Index	Combination Effects (Number of Bacterial Strains (%))			
				Synergistic Effect	Additive Effect	Indifference	Antagonistic Effect
5.5	AMPC	27	—	1 (3.7*)	13 (48.1)	13 (48.1)	0 (0)
	CAM	27		10 (37.0)	17 (63.0)	0 (0)	0 (0)
7.17	AMPC	27	—	1 (3.7)	25 (92.6)	1 (3.7)	0 (0)
	CAM	27		15 (55.6)	12 (44.4)	0 (0)	0 (0)

AMPC: amoxicillin, CAM: clarithromycin

* The total percentage was 99.9% due to rounding.

The data in the above table demonstrate that rabeprazole seems to help clarithromycin more (many more strains with synergistic effect) than amoxicillin at pH 5.5. Most strains showed an additive effect or indifference with rabeprazole and amoxicillin at pH 5.5. The same was seen at pH 7.17, but more strains showed an additive effect with rabeprazole and amoxicillin and more showed synergy with rabeprazole and clarithromycin. This may be due to the fact that rabeprazole lowers the pH and these drugs, especially clarithromycin are more active as the pH increases. There was no antagonism between the drugs.

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TABLE 4
The Combination Effects of Amoxicillin and Clarithromycin
On *Helicobacter pylori*

PH of Medium	Number of Strains	Range of Σ FIC Index	Combination Effects (Number of Bacterial Strains (%))			
			Synergistic Effect	Additive Effect	Indifference	Antagonistic Effect
5.5	27	—	7 (25.9)	20 (74.1)	0 (0)	0 (0)
7.17	27		1 (3.7)	26 (96.3)	0 (0)	0 (0)

The above table shows that for most strains the combination of amoxicillin and clarithromycin is additive. Rabeprazole seems to be needed to get synergistic effects. When added it seems to help clarithromycin more than amoxicillin.

Amoxicillin

Studies show that *Helicobacter pylori* is susceptible to ampicillin/amoxicillin *in vitro* with MIC₉₀ values between 0.004 and 0.12 µg/mL (7,8). These studies show that the activity of amoxicillin is reduced under acidic conditions. One study showed only a slight decrease in activity between testing at pH 7.2 and 5.5 (using amoxicillin) while the other study showed about a 10-fold decrease between pH 7.5 and 5.5 (using ampicillin). Amoxicillin is less ionized at acid pH and may, therefore, be less sensitive to low pH.

Clarithromycin

Clarithromycin MIC₉₀ values against *H. pylori* range from 0.03 to 0.06 µg/mL (9, 10). The 14-hydroxy metabolite of clarithromycin also exhibits good activity against *H. pylori* (MIC₉₀ = 0.06 µg/mL) and the combination of clarithromycin and its 14-hydroxy metabolite appear to be additive (7). The ability of clarithromycin to inhibit *H. pylori* is reduced under acidic conditions (9,10). Clarithromycin is about 8 to 16 times less active against *H. pylori* at pH 5.5 compared to pH 7.2. The 14-hydroxy metabolite retains most of its activity at pH 5.5.

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MECHANISM(S) OF RESISTANCE

Amoxicillin

Production of beta-lactamase usually accounts for the most frequent mechanism of resistance to this class of antibiotics. Such resistance has largely spread in various groups of bacteria but it has not been detected in clinical *H. pylori* isolates. This may relate to the fact that contacts and opportunities for genetic exchanges between *H. pylori* and other bacterial species are likely to be limited in the gastric mucosa environment. However, *in vitro* studies have shown that beta-lactamase genes have been transferred to *H. pylori* isolates (11).

A second mechanism of bacterial resistance to beta-lactams is modification of the bacterial cell wall target (i.e. the penicillin binding proteins [PBPs]). Successive mutations or repeated acquisition of foreign DNA by genetic transformation have resulted in modifications of the PBPs with a subsequent decrease in their affinity for antibiotics acting at the cell wall level. *Helicobacter pylori* has a high natural DNA transformation ability. One study (12) has reported finding a resistant mutant and transferring this resistance to susceptible isolates by transformation.

Until recently there were no published reports of amoxicillin-resistant *H. pylori* isolates. Recently, there have been some reports (13,14,12) of *H. pylori* resistance to amoxicillin. Amoxicillin-resistant isolates often lead to treatment failures. In the first study (13) pre-treatment amoxicillin resistance among *H. pylori* isolates from gastric antral biopsies was found in 31% (13 of 42) of cases. This study was done in Italy. The MICs for these isolates were all greater than 256 µg/mL. These amoxicillin-resistant isolates were eradicated in only four of the 13 patients with resistant strains. The cure rate for sensitive strains was 66%. The mechanism of amoxicillin resistance appeared to be related to the development of tolerance since the antibiotic phenotype was lost on freezing or storage.

In the second report (14) amoxicillin resistant *H. pylori* were isolated from four patients in the USA. The MICs for these strains were > 256 µg/mL. Beta-lactamase activity was not detected in these isolates. Complete loss of the resistant phenotype was seen after the strains were stored at -80°C. Some degree of amoxicillin resistance in the initially resistant strains could be rescued by plating the strains on plates containing amoxicillin.

In the third report (12) a stable resistance mechanism was easily transferred through DNA exchange by natural transformation and conjugation. In this report an amoxicillin-resistant *H. pylori* isolate was found in a patient with chronic obstructive pulmonary disease that had twelve courses of amoxicillin over the past six years. Resistance to amoxicillin remained stable after repeated cycles of storage at -80°C and after repetitive subculture on amoxicillin free agar. DNA from this strain was able to transform amoxicillin-susceptible strains at a frequency of one per 100,000. The MIC of the resistant strain was 400-fold higher than the MIC of the susceptible strain.

Clarithromycin

Resistance of *Helicobacter pylori* to clarithromycin is prevalent throughout the world. Rates vary in each study. Glupczynski reported in 1998 that resistance rates vary from country to country, and resistance appears to be on the increase when comparing rates between 1991-1994 and 1995-1997 (15). Resistance rates in the United States increased from 3.8% to 12.6% and in Spain from 0% to 12% during these two testing periods. Megraud reported in 1998 that resistance to clarithromycin is due to a decrease in binding to ribosomes associated with a point mutation on the 23S rRNA with the rate in Europe varying from 0% to 15% (16). The mutation is an A=G transition mutation in base-pair 2143 or 2144 but in a few cases it may be a A=C transversion mutation in base-pair 2143. Such point mutations result in a decreased affinity between the ribosomes and clarithromycin and in a marked increase in the MIC values. A2143G mutations are usually associated with higher resistance levels (MIC \geq 64 μ g/mL) than those of the A=G type located at position 2144 (MIC \geq 32 μ g/mL). Resistance to clarithromycin is crossed to all other macrolides and it stably persists over time *in vivo* and also after multiple *in vitro* subcultivation. Peterson et al. (11) reported that 12% of patients are infected with clarithromycin-resistant organisms before treatment, and that resistant strains are isolated from 21% of patients after treatment with clarithromycin alone.

PRECLINICAL EFFICACY (IN VIVO)

PHARMACOKINETICS/BIOAVAILABILITY

The dosage regimen in this application is rabeprazole 20 mg twice a day in combination with amoxicillin 1000 mg twice a day and clarithromycin 500 mg twice a day for 7 days.

The information in this section is taken from the NDA studies submitted by the applicant and had not been reviewed by a Biopharmaceutical Reviewer at the time this review was written.

After oral administration of 20 mg rabeprazole sodium peak plasma concentrations (C_{max}) of rabeprazole occur over a range of 2.0 to 5.0 hours. The rabeprazole C_{max} and AUC are linear over an oral dose range of 10 mg to 40 mg. The plasma half-life ranges from 1 to 2 hours. Peak plasma concentrations (C_{max}) at steady state after oral doses of 10, 20, and 40 mg were 202, 402, and 960 ng/mL.

Following oral administration of 20 mg, rabeprazole is absorbed and can be detected in plasma by one hour. Absolute bioavailability for a 20-mg oral tablet of rabeprazole (compared to intravenous administration) is approximately 52%.

Following a single 20-mg oral dose of ¹⁴C-labeled rabeprazole, approximately 90% of the drug was eliminated in the urine, primarily as thioether carboxylic acid; its glucuronide, and mercapturic acid metabolites. The remainder of the drug was recovered in the feces. No unchanged rabeprazole was recovered in the urine or feces.

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Rabeprazole is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. *In vitro* studies have demonstrated that rabeprazole is primarily metabolized in the liver by cytochromes P450 3A (sulphone metabolite) and 2C19 (desmethyl rabeprazole). The thioether metabolite is formed by reduction of rabeprazole.

An open label, four-way crossover pharmacokinetic study was performed to evaluate the interaction between rabeprazole, clarithromycin, and amoxicillin in sixteen healthy volunteers. Subjects received either monotherapy with one of the three drugs or combination therapy with all three. A single dose was given on Day 1 and Day 7. Twice a day dosing was used on Days 2 to 6. Dosages were the same as the proposed doses for each of the drugs that will be used for the eradication of *Helicobacter pylori*. The results are summarized in TABLE 5.

TABLE 5
Pharmacokinetic Interaction between Rabeprazole,
Clarithromycin, and Amoxicillin

Drug	Pharmacokinetic Parameter	Geometric Mean		Treatment Ratio	
		Triple Therapy ^a	Monotherapy ^b	Point Estimate	95% Confidence Interval
Clarithromycin	C _{max} (µg/mL)	3.14	3.15	1.00	0.87-1.14
	AUC (µg.h/mL)	23.79	23.15	1.03	0.91-1.16
14-Hydroxy Clarithromycin	C _{max} (µg/mL)	1.06	0.72	1.46	1.33-1.60
	AUC (µg.h/mL)	9.54	6.71	1.42	1.31-1.54
Amoxicillin	C _{max} (µg/mL)	12.43	11.39	1.09	0.99-1.20
	AUC (µg.h/mL)	37.52	39.39	0.95	0.90-1.01
Rabeprazole	C _{max} (Ng/mL)	348	260	1.34	1.04-1.71
	AUC (Ng.h/mL)	512	462	1.11	0.90-1.37

^aTriple-therapy = clarithromycin 500 mg, amoxicillin 1000 mg, and rabeprazole 20 mg

^bMonotherapy with either clarithromycin 500 mg, amoxicillin 1000 mg, or rabeprazole 20 mg

The data in the above table demonstrate that the AUC and C_{max} for clarithromycin and amoxicillin were similar during triple-therapy compared to monotherapy. The rabeprazole AUC and C_{max} increased by 11% and 34%, respectively, and the 14-hydroxyclarithromycin (active metabolite of clarithromycin) AUC and C_{max} increased by 42% and 46%, respectively, during the triple-therapy compared to values obtained during monotherapy.

ANIMAL MODELS

Most animal models are not adequate for the study of *Helicobacter pylori* gastrointestinal infection. *H. pylori* infections have been established in piglets (17) and rats (18); however, these species do not develop ulcers. Ferrets are known to develop gastritis and ulcers as a natural disease. The disease appears to be associated with *Helicobacter mustelae* infection (19). The obvious limitation of the ferret model is that *H. pylori* is not the organism involved, thus the relevance to human disease is unclear.

A study was performed (20) in gerbils to determine the effect of rabeprazole with amoxicillin and clarithromycin in the eradication of *Helicobacter pylori* from the stomach of experimentally infected animals. Groups of fasted Mongolian gerbils were infected by the oral administration of *H. pylori* ATCC 43504. Prior to therapy, the animals were divided into groups of 11 or 12 animals. Antibacterial therapy (diluent in control animals) was administered twice daily for 3 days. Rabeprazole was dosed at 6 mg/kg by the subcutaneous route. Amoxicillin was given orally at a dose of 3 mg/kg and clarithromycin was given orally at a dose of 0.8 mg/kg. The post-treatment number of viable bacteria remaining in the stomachs of infected animals five days after cessation of treatment was assessed by plate counts. Results are shown in TABLE 6.

TABLE 6
Effect of Rabeprazole and Antibiotics Alone Or In Combination
on *H. pylori* Eradication from Gerbil Gastric Mucosa

Treatment	Number of Viable Cells (Log CFU/g of tissue)
Control	6.2
Rabeprazole Alone	6.2
Amoxicillin plus Clarithromycin	4.4
Rabeprazole plus Amoxicillin and Clarithromycin	2.1

These data demonstrate that rabeprazole alone was no better than placebo in eradicating *Helicobacter pylori* from gerbil stomachs. Treatment with amoxicillin plus clarithromycin produced about a 100-fold reduction in the number of viable cells of *H. pylori* in the gastric mucosa of gerbils as compared to untreated controls. When therapy was augmented with rabeprazole the bacterial count was 10,000-fold less than those in controls, or a 100-fold greater reduction than produced in the group treated with amoxicillin plus clarithromycin without rabeprazole.

CLINICAL EFFICACY (CLINICAL MICROBIOLOGY)

Three clinical trials were performed which determined the efficacy and safety profile of rabeprazole, amoxicillin, clarithromycin triple therapy for the eradication of *Helicobacter pylori*.

STUDY E3810-E044-602

A Pilot Study to Compare the Efficacy and Safety Profile of Four Treatment Regimens for the Eradication of *Helicobacter pylori* Patients with Chronic Antral Gastritis or Peptic Ulcer Disease

This was a single center pilot study conducted in Europe to determine the eradication potential of rabeprazole triple therapy and dual therapy. Adult outpatients with chronic gastritis with or without peptic ulcer disease who had a positive biopsy urease test (CLOtest) for *Helicobacter pylori* at endoscopy were recruited. Eight gastric mucosal biopsies were taken at the pre-treatment visit. Two antral biopsies were used for the urease test, 2 antral and 2 corpus biopsies were used for histopathology and 1 antral and 1 corpus biopsy were used for microbiology cultures. To be eligible patients also required a positive ¹³C-Urea Breath Test (¹³C-UBT). This was a double-blind, randomized, parallel-group comparison in which eligible patients were randomized to receive one of the following four treatment regimens for seven days:

1 (RAC)	Rabeprazole 20 mg bid Amoxicillin 1000 mg bid Clarithromycin 500 mg bid
2 (RAM)	Rabeprazole 20 mg bid Amoxicillin 1000 mg bid Metronidazole 400 mg bid
3 (RCM)	Rabeprazole 20 mg bid Clarithromycin 500 mg bid Metronidazole 400 mg bid
4 (RC)	Rabeprazole 20 mg bid Clarithromycin 500 mg bid

Efficacy was based on the presence or absence of *H. pylori* post-treatment. ¹³C-UBT tests were performed 5 and 9 weeks after the start of therapy. Patients with a positive ¹³C-UBT test at either follow-up visit underwent another endoscopy at which biopsies were taken for *H. pylori* status by urease test, histopathological identification, and microbiological cultures. Patients who were positive at 5 weeks were not retested at week 9. All 75 randomized patients were included in the intent-to-treat (ITT) population. There were 70 patients in the per-protocol (PP) population. Three patients took less than 6 days of medication and 2 took prohibited antibiotics.

Helicobacter pylori eradication rates for the two efficacy populations are shown in TABLE 7.

TABLE 7
 Eradication Rates for *Helicobacter pylori* (Study-602)

Treatment	Intent-to-Treat		Per-Protocol	
	No. Patients	% Patients	No. Patients	% Patients
RAC	18/19	94.7	18/18	100.0
RAM	17/19	89.5	15/17	88.2
RCM	18/18	100.0	17/17	100.0
RC	12/19	63.2	12/18	66.7
Overall	65/75	86.7	62/70	88.6

The patient in the ITT population who failed RAC treatment took only one dose of study medication. The two patients who failed RAM treatment had strains with metronidazole MICs of >8 µg/mL (32 and >32 µg/mL). None of the pre-treatment *H. pylori* isolates from the six patients who failed RC treatment were clarithromycin resistant, but 4 of the five who were successfully cultured post-treatment had developed clarithromycin resistant (0.016 µg/mL→24 µg/mL; 0.016 µg/mL→8 µg/mL; 0.016 µg/mL→4 µg/mL; 0.047µg/mL→0.5 µg/mL). This development of resistance to clarithromycin is well known when using treatments containing only clarithromycin and a proton-pump inhibitor. This dual therapy is not as effective as the triple therapy regimens. All but one of the eradication failures was positive for *H. pylori* at the week 5 visit. The remaining failure was negative at week 5 but reverted to positive at week 9.

Susceptibility to amoxicillin, metronidazole, and clarithromycin were determined by E-test. Breakpoints used were as follows; amoxicillin susceptible, MIC ≤0.25 µg/mL, resistant, MIC >0.25 µg/mL; clarithromycin susceptible, MIC ≤0.1 µg/mL, resistant MIC >0.1 µg/mL; metronidazole susceptible, MIC ≤8 µg/mL, resistant >8 µg/mL. Initially the antral biopsies were cultured. Corpus biopsies were only cultured if the antral cultures were negative. To be considered evaluable a patient had to be *H. pylori* positive on histopathology and/or culture. The E-test is not an approved NCCLS susceptibility test method for *H. pylori*. The breakpoints used for clarithromycin are also not the approved NCCLS breakpoints of susceptible ≤0.25 µg/mL, intermediate 0.5 µg/mL, and resistant ≥1.0 µg/mL.

Pre-treatment, all randomized patients were *H. pylori* positive on urease test (CLOtest), ¹³C-UBT and histopathology. *Helicobacter pylori* was also cultured in all but four cases.

Post-treatment, while ¹³C-UBT was conducted on all patients, only the eradication failures were endoscoped and, therefore, had biopsies for urease tests, histopathology and culture. In all eradication failures, positive ¹³C-UBT post-treatment was confirmed by positive histopathology in all cases, by positive culture in all but one case, and by positive urease test in all but three cases.

TABLE 8 shows the MICs for each of the three antimicrobials for each of the four treatments.

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TABLE 8
Helicobacter pylori MIC Values (Study 602)

MIC (µg/mL)	Number of Isolates at each MIC											
	RAC			RAM			RCM			RC		
	Amox	Metr	Clar	Amox	Metr	Clar	Amox	Metr	Clar	Amox	Metr	Clar
<0.016	4			1		1	2		2	6****+		
0.016	7		10	10++		9	6		9	10****+		9****+
0.023	2		3	5*		3*	4			1		3*
0.032	3		1	1	1+	2+	1		3	3*		1
0.047				1*	1		4			3+	1	2*
0.064	2		1						1	2		2
0.094											1+	
0.125		2	1				1				2++	1
0.19		1	1		1				1			1
0.25		1	1		3	2*		2	1			
0.38		1			1			1	1		2*+	
0.5		2						2			3*	1+
0.75		1			1			1				
1		2				1+		2			2*	
1.5		1			2						1	
2		2			3			3			4*	
3								1			1	
4					1			1				1+
6		1									1	
8											1	1+
12								1				
24												1+
32					1*	1					1*	
>32		4			3*+			4			4*+	

Amox = amoxicillin; Metr = metronidazole; Clar = clarithromycin

* represents a pre-treatment MIC from an isolate that failed treatment

+ represents a post-treatment MIC value from a patient who failed

All amoxicillin MIC were ≤ 0.064 µg/mL. The metronidazole MIC varied from 0.032 µg/mL to ≥ 32 µg/mL. Many isolates with MICs of ≥ 32 µg/mL were eradicated. Almost all pre-treatment clarithromycin MICs were ≤ 0.38 µg/mL. After treatment failure, especially with rabeprazole and clarithromycin alone, MIC values increased to ≥ 0.5 µg/mL.

STUDY E3810-E044-603
A Multi-Center Study to Compare the Efficacy and Safety Profile of Two Rabeprazole and Two Omeprazole Triple Therapy Regimens Administered For 7 Days for the Eradication of *Helicobacter pylori* in Subjects with Documented Peptic Ulcer Disease and *Helicobacter pylori* Infection

This was a double-blind, parallel group comparison of rabeprazole and omeprazole triple therapy in patients with *H. pylori* associated peptic ulcer disease (active or history within the past five years) conducted in Europe. Treatment was for 7 days with a follow-up period of 12 weeks. Patients with confirmed *H. pylori* infection were randomized to receive one of the following regimens:

1. (RAC) Rabeprazole 20 mg bid + amoxicillin 1000 mg bid + clarithromycin 500 mg bid
2. (RCM) Rabeprazole 20 mg bid + clarithromycin 500 mg bid + metronidazole 400 mg bid
3. (OAC) Omeprazole 20 mg bid + amoxicillin 1000 mg bid + clarithromycin 500 mg bid
4. (OCM) Omeprazole 20 mg bid + clarithromycin 500 mg bid + metronidazole 400 mg bid

Follow-up visits were at Week 5 (four weeks post-treatment) and at Week 13 (12 weeks post-treatment) if applicable. Subjects confirmed as positive at week 5 by ¹³C-UBT were not retested at week 13.

Subjects had to undergo an gastrointestinal endoscopy, with eight biopsies being taken, between four hours and 14 days prior to the rest of the screening assessments. Two antral biopsies were used for urease tests (CLOtest). Two antral and two corpus biopsies were used for histology evaluations. One antral and one corpus biopsy were used for microbiological analysis. Isolates were tested using the E-test system for sensitivity to clarithromycin, amoxicillin, and metronidazole and by the agar dilution method for sensitivity to clarithromycin and metronidazole.

Subjects without an active ulcer at screening and a positive ¹³C-UBT at Week 5 were to have a further endoscopy no more than 14 days after the Week 5 visit. Subjects with an active ulcer at screening and a positive ¹³C-UBT at Week 5 were to have a further endoscopy up to seven days thereafter. Subjects with a negative ¹³C-UBT at Week 5 were to have the test repeated at Week 13; if the result was positive at Week 13, subjects were to undergo an endoscopy. Successful eradication of *H. pylori* was defined as a negative ¹³C-UBT at both the Week 5 and Week 13 post-treatment assessment.

There were 348 subjects randomized in the study. Three did not receive treatment. Of those subjects randomized and treated, 42 were withdrawn. TABLE 9 shows the numbers of subjects included in the safety, ITT (intent-to-treat) and PP (per-protocol) populations.

TABLE 9
Number of Subjects Included in Safety, ITT, and PP Populations
(Study 603)

	RAC	OAC	RCM	OCM	All Regimens
Evaluable for safety	87	86	85	87	345
Evaluable for ITT	83	85	81	85	334
Evaluable for PP	65	63	61	66	255

Only 11 patients were excluded from the ITT population, in all cases due to a negative ¹³C-UBT test. Ninety patients were excluded from the PP population, the main reason being the use of a prohibited medication (57 subjects) or a negative ¹³C-UBT test at Week 5 with no follow-up at Week 13 (18 subjects). TABLE 10 shows the eradication rates for each of the four treatment groups in the ITT population and the per-protocol (PP) population.

TABLE 10
Helicobacter pylori Eradication Rate For the ITT Population
(Study 603)

Treatment Group	ITT Population	PP Population
RAC	70/83 (84%)	61/65 (94%)
OAC	61/85 (72%)	53/63 (84%)
RCM	56/81 (69%)	48/61 (79%)
OCM	67/85 (79%)	57/66 (86%)

From the above data it appears that rabeprazole is at least as good as omeprazole in eradicating *H. pylori* when combined with amoxicillin and clarithromycin. When combined with metronidazole and clarithromycin, omeprazole appears to be better than rabeprazole.

TABLE 11 shows the population of subjects sensitive to the antibiotics, and further classified as sensitive to either, both, or only one of the antibiotics to which they were randomized. The percentage eradicated is calculated as a percentage of the number of subjects in that particular sensitivity classification. Breakpoints used were as follows; amoxicillin susceptible, MIC ≤ 0.25 $\mu\text{g/mL}$, resistant MIC > 0.25 $\mu\text{g/mL}$; clarithromycin susceptible, MIC ≤ 0.1 $\mu\text{g/mL}$, resistant MIC > 0.1 $\mu\text{g/mL}$; metronidazole susceptible, MIC ≤ 8 $\mu\text{g/mL}$, resistant > 8 $\mu\text{g/mL}$. Testing was performed by E-test methodology. This test method and the above breakpoints are not those approved by NCCLS.

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TABLE 11
Eradication Rate by Antibiotic Sensitivity at Screening
Pre-Protocol Population (Study 603)

Micro Results	RAC N=65		OAC N=63		RCM N=61		OCM N=66	
	No. of Subjects	% Eradication						
Sens	55	95	57	88	50	80	61	85
Fully	52	94	54	93	39	79	44	91
Partial	3	100	3	0	11	82	17	71
C-sens	1	100	0	0	8	88	13	85
C-res	2	100	3	0	3	67	4	25
Resistant	0	0	0	0	1	0	0	0
Unknown	10	90	6	50	10	80	5	100
Total		94		84		79		86

Micro--Microbiology

Sens--Sensitive

Fully--sensitive to both antibiotics received

Partially--sensitive to one of the antibiotics received and resistant to the other

C-sens--sensitive only to clarithromycin and resistant to the other antibiotic

C-res--sensitive only to amoxicillin/metronidazole and resistant to clarithromycin

The number of subjects with isolates sensitive to one or more of the antibiotics was similar in each of the four treatment groups, as was the percentage eradication. In all groups the majority of subjects had isolates that were fully sensitive at screening. The metronidazole treatment groups had a lower percentage of subjects with fully sensitive isolates than did subjects in the amoxicillin treatment groups. There was a lower eradication rate in clarithromycin resistant isolates than for sensitive isolates. Sensitivity was unknown in a number of subjects

TABLE 12 shows the MICs for each of the three antimicrobials for each of the four treatments.

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TABLE 12
Helicobacter pylori MIC Values (Study 603)

MIC (µg/mL)	Number of Isolates at each MIC											
	RAC			RCM			OAC			OCM		
	Amox	Metr	Clar	Amox	Metr	Clar	Amox	Metr	Clar	Amox	Metr	Clar
<0.016	65 (10*)++	2*	20*	63 (21*)++	5*	20 (4*)	70 (15*) 8+	2	16 (6*)	68 (11*) (5+)	2*	19 (4*)
0.016	1	5	14*** +	4	2	21 (8*)	6**	3*	28** +++	4*	6**	20**
0.023	1		7**	1+	3*	8***	4*	4	9***	2*	3*	9*
0.032	1	7*	11**	1*	3*	7*		3**	8+		5	8*
0.047	1	5*	9*		1	2*	1*	8**	6***		2*	9*
0.064		6*	4*		3*	2*		3+	5*		5*	
0.094		5	1		3	1*	1	7*	3+		4*	
0.125		4**			6****			6*			5	
0.19		3			6***			3*			4*	
0.25		6+			3*			8**		1	4*	
0.38		3*	1		3**			5+	1*		2*	
0.5	1	4			4*			3*			1*	
0.75		2*			4*			3			5	1
1		2			2			1			2	
1.5		2			3+			4**+			4	
2					2						1	
3									1+			
4		1										1+
6		1				1*		2				
8					2*	1*			2**		1	
12					1						2+	1*
16						1+		1+				
24					1*			1			2*+	
32					1						1	
48		1*						1+			1	2*+
64					1*	1+		2+	2*+		2	2*+
96		2*			1							
128					1			1*			1*	
192					1							
256								1*				
>256		9+	3+		8 (3*) ++	4**		10 (4*) (2+)	1+		10 (3*) (3+)	3* (2+)

Amox = amoxicillin; Metr = metronidazole; Clar = clarithromycin

* represents a pre-treatment MIC from an isolate that failed treatment

+ represents a post-treatment MIC value from a patient who failed

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All amoxicillin MIC except one at 0.5 µg/mL were ≤0.25 µg/mL. The metronidazole MIC varied from <0.016 µg/mL to ≥256µg/mL. Many isolates with metronidazole MICs of ≥256 µg/mL were eradicated. Almost all pre-treatment clarithromycin MICs were ≤0.38 µg/mL. Isolates with clarithromycin MICs ≥0.25 µg/mL tended to be failures.

There were only 16 subjects in the ITT population with both a pre-treatment and post-treatment *H. pylori* microbiology test result. Amoxicillin MICs did not change during treatment and were almost all <0.016 µg/mL. Although MICs increased for metronidazole and clarithromycin in some patients, isolates from other patients did not show any increase and some patients had isolates with lower MIC values after treatment. TABLE 13 shows the MICs for the isolates from these patients both pre- and post-treatment

TABLE 13
MIC values for *Helicobacter pylori* before and after Treatment

Treatment	Patient #	Amoxicillin MIC (µg/mL)		Metronidazole MIC (µg/mL)		Clarithromycin MIC (µg/mL)	
		Pre Treatment	Post treatment	Pre Treatment	Post treatment	Pre Treatment	Post treatment
RAC	371	<0.016	<0.016	0.064	0.25	0.023	0.016
	415	<0.016	<0.016	<0.016	>256	<0.016	>256
RCM	341	<0.016	<0.016	0.5	>256	0.016	64
	684	<0.016	<0.016	0.125	1.5	0.016	>256
OAC	126	0.016	<0.016	1.5	1.5	0.38	64
	136	<0.016	<0.016	128	>256	8	3
	248	<0.016	<0.016	256	0.38	<0.016	0.032
	264	<0.016	<0.016	>256	>256	0.064	0.016
	315	0.047	<0.016	1.5	0.064	64	0.094
	673	<0.016	<0.016	0.25	16	<0.016	0.016
	680	<0.016	0.016	>256	64	8	>256
OCM	111	<0.016	<0.016	0.19	12	<0.016	4
	273	<0.016	<0.016	0.094	>256	48	48
	570	<0.016	<0.016	24	24	0.047	>256
	623	<0.016	<0.016	0.25	>256	12	>256
	666	<0.016	<0.016	128	>256	0.016	64

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STUDY E3810-A001-604
Comparison of the Efficacy and Safety of Three
Rabeprazole-based Triple Therapy Regimens to Omeprazole-based
Triple Therapy for Eradication of *Helicobacter pylori*

This was a multi-center, double-blind, randomized, stratified, parallel group study designed to compare four *Helicobacter pylori* eradication regimens in approximately 800 patients with confirmed *H. pylori* infection. Patients were randomized into four treatment groups, with 1:1 stratification of peptic ulcer disease (PUD) patients and non-peptic ulcer disease (NPUD) patients who had undergone clinically indicated upper gastrointestinal endoscopy because of gastrointestinal symptoms and/or finding on physical examination.

Each treatment group consisted of approximately 200 patients. Forty-five United States centers participated in the study. The study consisted of a screening period, a treatment period of 10 days, and a post-treatment assessment at least six weeks after completion of the treatment period.

To be included in the study patients had to have an upper GI endoscopy indicated because of gastrointestinal symptoms and/or finding on physical examination, and have a positive *H. pylori* antibody test and *H. pylori* infection documented by ¹³C-UBT and either urease CLOtest or culture.

Eligible patients were randomized in a stratified 1:1 (PUD:NPUD) ratio to receive one of the following four regimens:

1. (RAC-3) Rabeprazole 20 mg bid + clarithromycin 500 mg bid + amoxicillin 1000 mg bid for 3 days followed by matching placebo tablets and capsules for seven days.
2. (RAC-7) Rabeprazole 20 mg bid + clarithromycin 500 mg bid + amoxicillin 1000 mg bid for 7 days followed by matching placebo tablets and capsules for three days.
3. (RAC-10) Rabeprazole 20 mg bid + clarithromycin 500 mg bid + amoxicillin 1000 mg bid for 10 days.
4. (OAC-10) Omeprazole 20 mg bid + clarithromycin 500 mg bid + amoxicillin 1000 mg bid for 10 days.

Qualified participants were assigned unique treatment randomization numbers in sequential order at each site. The PUD patients were allocated numbers between 1 and 400, and the NPUD patients were allocated numbers between 401 and 800.

At the screening visit patients were tested for *Helicobacter pylori* antibody with the FlexSure® HP serum test. Patients with a positive antibody test continued to be screened for study entry. A ¹³C-Urea Breath Test (¹³C-UBT) and endoscopy were performed in patients with a positive antibody test. Biopsies of the stomach, five from the antrum and three from the corpus were obtained. Two antral biopsies were used for CLO testing. One antral and one corpus biopsy were used for cultures. Positive *H. pylori* strains were screened for antibiotic sensitivity to clarithromycin and amoxicillin using the NCCLS agar dilution method. Two antral and two corpus biopsies were used for histology.

A Day 11-15 visit was performed. This visit included a physical examination, laboratory determinations, assessment of adverse events and concomitant medications, symptom assessment, and medication compliance assessment.

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Post-treatment assessments were performed at least six weeks but not more than 10 weeks after completion of the treatment period. All patients had a ¹³C-UBT performed at the post-treatment assessment. If the ¹³C-UBT was positive, the patient underwent a follow-up endoscopy and biopsies were taken for histology, CLO test, and microbiology assessments. These biopsies were used to confirm the presence of *H. pylori* and to assess whether the organism had acquired resistance to the antibiotics used.

Patients with an ulcer at study entry had a repeat endoscopy performed at the post-treatment visit to document ulcer status.

Efficacy assessments were based on patient disposition with regards to the presence/absence of *H. pylori* infection based on the ¹³C-UBT at the ≥6 week post-treatment measurement.

A summary of patient disposition is presented in TABLE 14.

TABLE 14
Summary of Patient Disposition—All Randomized Patients (Study 604)

	RAC 3-day (N=194)	RAC 7-day (N=200)	RAC 10-day (N=202)	OAC 10-day (N=207)	Total (N=803)
All Randomized Patients	194 (100%)	200 (100%)	202 (100%)	207 (100%)	803 (100%)
Safety Patients	188 (97%)	195 (98%)	198 (98%)	207 (100%)	788 (98%)
Intent-to-Treat Patients (ITT)	187 (96%)	194 (97%)	196 (97%)	206 (99%)	783 (98%)
Per Protocol Patients (PP)	167 (86%)	166 (83%)	171 (85%)	179 (86%)	683 (85%)
Completed	161 (83%)	172 (86%)	174 (86%)	184 (89%)	691 (86%)
Discontinued Study	33 (17%)	28 (14%)	28 (14%)	23 (11%)	112 (14%)
Death	0	0	0	0	0
Adverse Event	8 (4%)	8 (4%)	4 (2%)	6 (3%)	26 (3%)
Patient Withdrew Consent	5 (3%)	1 (<1%)	4 (2%)	4 (2%)	14 (2%)
Protocol Violation	5 (3%)	4 (2%)	10 (5%)	5 (2%)	24 (3%)
Lost of Follow-Up	13 (7%)	12 (6%)	8 (4%)	7 (3%)	40 (5%)
Other	2 (1%)	3 (2%)	2 (<1%)	1 (<1%)	8 (<1%)

A total of 803 patients were randomized in this study. A total of 112 (14%) patients discontinued, 26 (3%) of them due to adverse events. A total of 20 (2%) of the randomized patients were excluded from the ITT population and 120 (15%) patients were excluded from the PP patient population. The most frequent reasons for exclusion were ¹³C-UBT missing/not determined at ≥42 days after the end of treatment (8% of patients) and early withdrawal for reasons other than study drug-related adverse events (9% of patients). A listing of patient evaluability is presented in TABLE 15.

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TABLE 15
Summary of Patient Evaluability—All Randomized Patients (Study 604)

	RAC 3-day (N=194)	RAC 7-day (N=200)	RAC 10-day (N=202)	OAC 10-day (N=207)	Total (N=803)
All Randomized Patients	194 (100%)	200 (100%)	202 (100%)	207 (100%)	803 (100%)
Safety Patients	188 (97%)	195 (98%)	198 (98%)	207 (100%)	788 (98%)
Intent-to-Treat Patients (ITT)	187 (96%)	194 (97%)	196 (97%)	206 (99%)	783 (98%)
Per Protocol Patients (PP)	167 (86%)	166 (83%)	171 (85%)	179 (86%)	683 (85%)
Excluded from Intent-to-Treat	7 (4%)	6 (3%)	6 (3%)	1 (<1%)	20 (2%)
Did not get any medication	6 (3%)	5 (3%)	4 (2%)	0	15 (2%)
Negative ¹³ C-UBT at screening	1 (<1%)	0	0	0	1 (<1%)
Missing ¹³ C-UBT at screening	0	0	1 (<1%)	1 (<1%)	2 (<1%)
Diagnostic criteria not met	6 (3%)	6 (3%)	5 (2%)	0	17 (2%)
Excluded from Per-Protocol	27 (14%)	34 (17%)	31 (15%)	28 (14%)	120 (15%)
¹³ C-UBT missing at ≥42 days	15 (8%)	13 (7%)	17 (8%)	21 (10%)	66 (8%)
Compliance violation	1 (<1%)	4 (2%)	2 (<1%)	2 (<1%)	9 (1%)
Early withdrawal (Not AE)	21 (11%)	16 (8%)	17 (8%)	15 (7%)	69 (8%)
Negative ¹³ C-UBT within 42 days from end of treatment without a ¹³ C-UBT ≥42 days	2 (1%)	3 (2%)	5 (2%)	6 (3%)	16 (2%)
Disallowed medication	10 (5%)	15 (8%)	15 (7%)	7 (3%)	47 (6%)

Patients may have had more than one reason for exclusion.

The eradication rate for patients with peptic ulcer disease (PUD) was about the same as for the patients without peptic ulcer disease (NPUD). In the ITT population 247/392 (63%) non-ulcer patients had *Helicobacter pylori* eradicated and 258/391 (66%) ulcer patients had *H. pylori* eradicated. The eradication rates in the per-protocol (PP) population were 238/346 (69%) in the non-ulcer patients and 245/337 (73%) in the ulcer patients. TABLE 16 shows the eradication rate by treatment group for the non-ulcer patients and the ulcer patients.

TABLE 16
Summary of Overall Eradication Rate by Treatment-ITT Population
(Study 604)

Treatment	Eradication	NPUD N (%)	PUD N (%)
RAC 3-day	Yes	27 (28%)	24 (27%)
	No	70 (72%)	66 (73%)
RAC 7-day	Yes	68 (73%)	82 (81%)
	No	25 (27%)	19 (19%)
RAC 10-day	Yes	78 (79%)	75 (77%)
	No	21 (21%)	22 (23%)
OAC 10-day	Yes	78 (79%)	75 (77%)
	No	29 (28%)	26 (25%)

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A summary of *Helicobacter pylori* outcome in the ITT population is presented in TABLE 17. A summary of *H. pylori* outcome in the PP population is presented in TABLE 18.

TABLE 17
Summary of *Helicobacter pylori* Outcome—ITT population
(Study 604)

Treatment	RAC N (%)		OAC N (%)	
	Eradicated	Not Eradicated	Eradicated	Not Eradicated
RAC 3-day vs OAC	51 (27%)	136 (73%)	151 (73%)	55 (27%)
RAC 7-day vs OAC	150 (77%)	44 (23%)	151 (73%)	55 (27%)
RAC 10-day vs OAC	153 (78%)	43 (22%)	151 (73%)	55 (27%)

TABLE 18
Summary of *Helicobacter pylori* Outcome—PP population
(Study 604)

Treatment	RAC N (%)		OAC N (%)	
	Eradicated	Not Eradicated	Eradicated	Not Eradicated
RAC 3-day vs OAC	50 (30%)	117 (70%)	146 (82%)	33 (18%)
RAC 7-day vs OAC	140 (84%)	26 (16%)	146 (82%)	33 (18%)
RAC 10-day vs OAC	147 (86%)	24 (14%)	146 (82%)	33 (18%)

The data in the above tables demonstrate that 3-day RAC treatment is not very successful in eradicating *H. pylori*. Both the 7-day and 10-day RAC treatments appear to be about equal in eradication rates and both seem to be very similar to the eradication rate seen with 10-day OAC treatment.

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Susceptibility Assessment

The National Committee for Clinical Laboratory Standards (NCCLS) methodology was used in this clinical trial. This agar dilution methodology is outlined in TABLE 19.

TABLE 19
NCCLS Recommended *H. pylori* Susceptibility Test Methodology.

Method	Agar Dilution
Medium	Mueller-Hinton agar + aged (≥ 2 week old) sheep blood (5% vol/vol)
Incubation	
Inoculation	

In vitro culture samples were to be assessed at Baseline and at the six week visit.

The NCCLS recommended clarithromycin breakpoints for agar dilution testing of *H. pylori* isolates were used in all studies. The amoxicillin breakpoints used were those approved by FDA and included in other labels for regimens that are used to eradicate *H. pylori*. TABLE 20 summarizes these testing criteria.

TABLE 20
MIC breakpoints for Amoxicillin and Clarithromycin
for Determining *H. pylori* Susceptibility Status

Susceptibility Status	Amoxicillin	Clarithromycin
Resistant	Not Defined	MIC ≥ 1 $\mu\text{g/mL}$
Intermediate	Not Defined	MIC = 0.5 $\mu\text{g/mL}$
Susceptible	MIC ≤ 0.25 $\mu\text{g/mL}$	MIC ≤ 0.25 $\mu\text{g/mL}$

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ACIPHEX® (rabeprazole sodium) for *H. pylori***PRETREATMENT CLARITHROMYCIN SUSCEPTIBILITY TESTING RESULTS**

There were clarithromycin MIC values available for 560 *Helicobacter pylori* isolates at baseline. TABLE 21 presents the distribution of MIC values for all four treatments combined. These data are shown graphically in Figure 1.

TABLE 21
Distribution of Baseline Clarithromycin MIC values (Study 604)

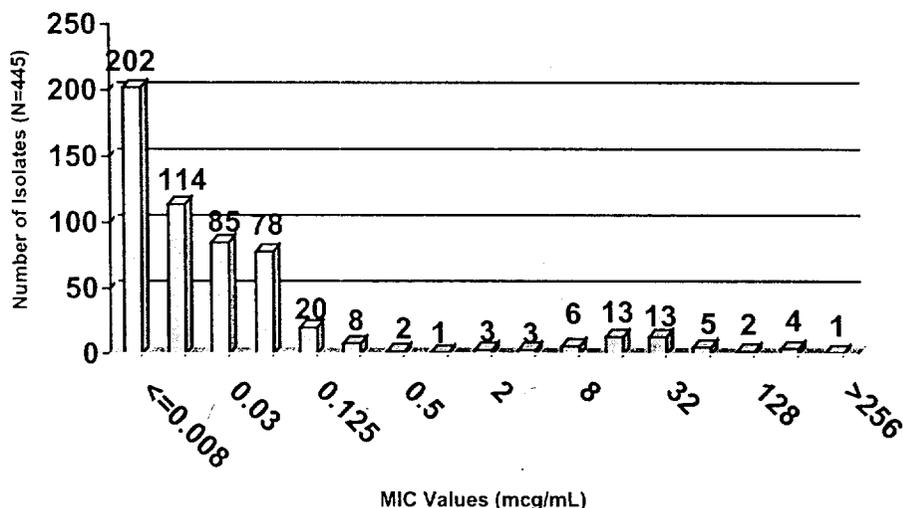
Baseline Clarithromycin MIC values (µg/mL)	Frequency	Percent	Cumulative Frequency	Cumulative Percent
≤ 0.008	202	36%	202	36%
0.015 (MIC ₅₀)	114	20%	316	56%
0.03	85	15%	401	72%
0.06	78	14%	479	86%
0.125	20	4%	499	89%
0.25 (MIC ₉₀)	8	1%	507	91%
0.5	2	<1%	509	91%
1	1	<1%	510	91%
2	3	1%	513	92%
4	3	<1%	516	92%
8	6	1%	522	93%
16	13	2%	535	96%
32	13	2%	548	98%
64	5	<1%	553	99%
128	2	<1%	555	99%
256	4	<1%	559	99.8%
>256	1	<1%	560	100%
Total	560			

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Figure 1
Distribution of Clarithromycin MIC Values for *H. pylori* (Baseline)
Study 604



The above data demonstrate that 90.5% (507/560) of the isolates were susceptible (MIC ≤0.25 µg/mL), <1% (2/560) were intermediate (MIC = 0.5 µg/mL), and 9.1% (51/560) were resistant (MIC ≥1 µg/mL) to clarithromycin at baseline. These data indicate that clarithromycin resistant *H. pylori* isolates are present in the general population. Susceptibility testing should be performed before treatment.

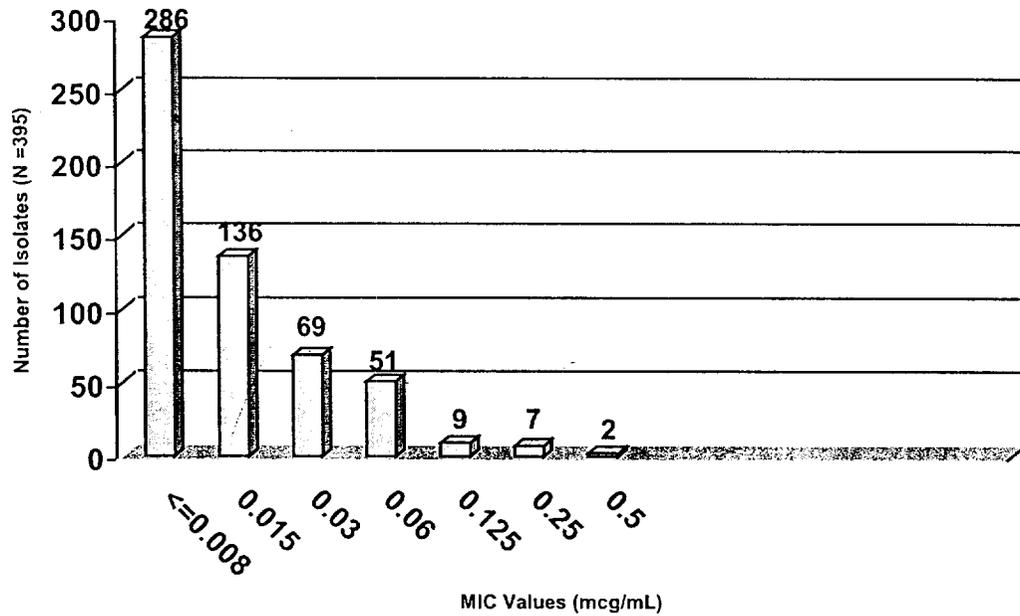
PRETREATMENT AMOXICILLIN SUSCEPTIBILITY TESTING RESULTS

The agar dilution baseline MIC value results for *Helicobacter pylori* susceptibility to amoxicillin are presented in TABLE 22. There were amoxicillin MIC values available for 560 *H. pylori* isolates at Baseline. Figure 2 shows the distribution of amoxicillin MICs at baseline in a graphic format.

TABLE 22
Distribution of Baseline Amoxicillin MIC values

Baseline Amoxicillin MIC values (µg/mL)	Frequency	Percent	Cumulative Frequency	Cumulative Percent
≤0.008 (MIC ₅₀)	286	51%	286	51%
0.015	136	24%	422	75%
0.03	69	12%	491	88%
0.06 (MIC ₉₀)	51	9%	542	97%
0.125	9	2%	551	98%
0.25	7	1%	558	>99%
0.5	2	<1%	395	100%

Figure 2
Distribution of Amoxicillin MIC Values for *H. pylori* (Baseline)
Study 604



These data indicate that the baseline amoxicillin MIC₅₀ value was ≤0.008 µg/mL and the baseline MIC₉₀ value was 0.06 µg/mL. There were only two patients with a baseline MIC that was not in the susceptible range for amoxicillin.

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ACIPHEX® (rabeprazole sodium) for *H. pylori***CLARITHROMYCIN SUSCEPTIBILITY TEST RESULTS AND BACTERIOLOGICAL OUTCOMES**

Table 23 presents the distribution of the baseline clarithromycin MIC values by the *Helicobacter pylori* eradication status at the Test-of-Cure (TOC) visit for all four treatment groups combined. A total of 9 of the 53 (17%) *H. pylori* isolates with baseline clarithromycin MIC values of ≥ 0.5 $\mu\text{g/mL}$ (classified as intermediate or resistant) were eradicated at the TOC visit.

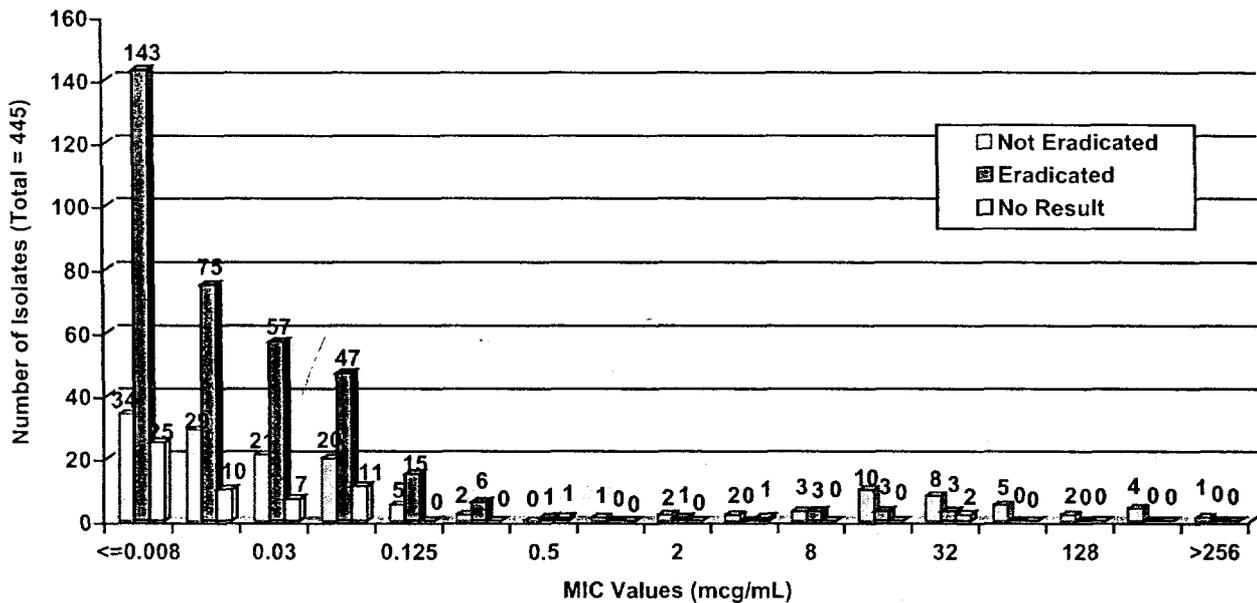
TABLE 23
Distribution of Baseline Clarithromycin MIC values for *H. pylori*
Based on Eradication Status at the Test-of-Cure (TOC) Visit (Number of Patients)
All Treatment Groups Combined (Study 604)

Baseline Clarithromycin MIC values ($\mu\text{g/mL}$)	TOC Visit <i>H. pylori</i> Status		
	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	No <i>H. pylori</i> Eradication Results
≤ 0.008	143 (70.8%)	34	25
0.015	75 (65.8%)	29	10
0.03	57 (67.1%)	21	7
0.06	47 (55.3%)	20	11
0.125	15 (75.0%)	5	0
0.25	6 (75.0%)	2	0
0.5	1 (50.0%)	0	1
1	0 (0.0%)	1	0
2	1 (33.3%)	2	0
4	0 (0.0%)	2	1
8	3 (50.0%)	3	0
16	3 (23.1%)	10	0
32	3 (23.1%)	8	2
64	0 (0.0%)	5	0
128	0 (0.0%)	2	0
256	0 (0.0%)	4	0
>256	0 (0.0%)	1	0
Total	354 (63.2 %)	149 (26.7%)	57 (10.2%)

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Figure 3 shows this data in a graphic format.

Figure 3
 Distribution of Baseline Clarithromycin MIC values
 By *H. pylori* Eradication Status at the TOC Visit All Treatments Combined



These data demonstrate that there are two populations of isolates based on clarithromycin MIC values. One population has clarithromycin MIC values of $\leq 0.25 \mu\text{g/mL}$ and most of these isolates are eradicated at the Test-of-Cure visit. The other population has higher MIC values and most of the isolates are not eradicated.

TABLE 24 shows the results by treatment group based on the baseline clarithromycin MIC value. This table shows that treatment for only 3 days was not long enough to get good eradication rates. Rabeprazole treatment with clarithromycin and amoxicillin for 7 or 10 days gave eradication rates similar to those seen with omeprazole plus clarithromycin and amoxicillin for 10 days. Most isolates with clarithromycin MICs in the resistant category ($\geq 1 \mu\text{g/mL}$) were not eradicated.

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TABLE 24
Distribution of Baseline Clarithromycin MIC values for *H. pylori* on Eradication Status at Week 6 Visit
All Available Data by Treatment Group

Week 6 Visit <i>H. pylori</i> Status												
Baseline Clarithromycin MIC values (µg/mL)	RAC 3-day			RAC 7-day			RAC 10-day			OAC 10-day		
	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing
≤0.008	11	24	7	51	3	6	46	3	7	35	4	5
0.015	7	20	1	20	4	2	27	3	2	21	2	5
0.03	10	15	2	21	1	2	15	4	1	11	1	2
0.06	3	15	3	10	2	4	16	1	1	18	2	3
0.125	1	4	0	2	0	0	5	0	0	7	1	0
0.25	1	0	0	0	1	0	3	1	0	2	0	0
0.5	0	0	1	0	0	0	0	0	0	1	0	0
1	0	0	0	0	0	0	0	0	0	0	0	1
2	0	0	0	0	1	0	0	0	0	1	1	0
4	0	0	0	0	1	0	0	0	0	0	1	1
8	0	1	0	1	2	0	0	0	0	2	0	0
16	0	3	0	3	0	0	0	3	0	0	4	0
32	0	3	0	1	2	1	1	1	0	1	2	1
64	0	1	0	0	2	0	0	1	0	0	1	0
128	0	0	0	0	0	0	0	1	0	0	1	0
256	0	1	0	0	1	0	0	2	0	0	0	0
>256	0	0	0	0	1	0	0	0	0	0	0	0
Total	33 (24.6%)	87 (64.9%)	14 (10.4%)	109 (75.2%)	21 (14.5%)	15 (10.3%)	113 (78.5%)	20 (13.9%)	11 (7.6%)	99 (72.3%)	20 (14.6%)	18 (13.1%)

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A summary of *Helicobacter pylori* outcome by sensitivity to clarithromycin at screening in the ITT population is presented in TABLE 25, and a summary of *H. pylori* outcome by clarithromycin sensitivity at screening in the per-protocol (PP) population is presented in TABLE 26.

TABLE 25
Summary of *Helicobacter pylori* Outcome by Clarithromycin Sensitivity at Screening
Intent-to-Treat Patients (ITT) (Study 604)

Treatment	Outcome	
	Eradicated	Not Eradicated
RAC 3-day (N=134)		
Sensitive	33 (27%)	91 (73%)
Intermediate	0	1 (100%)
Resistant	0	9 (100%)
RAC 7-day (N=145)		
Sensitive	104 (81%)	25 (19%)
Intermediate	0	0
Resistant	5 (31%)	11 (69%)
RAC 10-day (N=144)		
Sensitive	112 (83%)	23 (17%)
Intermediate	0	0
Resistant	1 (11%)	8 (89%)
OAC 10-day (N=137)		
Sensitive	94 (79%)	25 (21%)
Intermediate	1 (100%)	0
Resistant	4 (24%)	13 (76%)

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TABLE 26
 Summary of *Helicobacter pylori* Outcome by Clarithromycin Sensitivity at Screening
 Per Protocol (PP) Patients (Study 604)

Treatment	Outcome	
	Eradicated	Not Eradicated
RAC 3-day (N=121)		
Sensitive	32 (28%)	81 (72%)
Intermediate	0	0
Resistant	0	8 (100%)
RAC 7-day (N=119)		
Sensitive	95 (90%)	10 (10%)
Intermediate	0	0
Resistant	5 (36%)	9 (64%)
RAC 10-day (N=125)		
Sensitive	106 (91%)	10 (9%)
Intermediate	0	0
Resistant	1 (11%)	8 (89%)
OAC 10-day (N=122)		
Sensitive	93 (89%)	12 (11%)
Intermediate	1 (100%)	0
Resistant	3 (21%)	11 (79%)

These tables demonstrate that in the ITT patients with clarithromycin-sensitive *H. pylori*, the eradication rates were 27% in the 3-day RAC, 81% in the 7-day RAC, 83% in the 10-day RAC, and 79% in the 10-day OAC treatment groups. In the PP patients with clarithromycin-sensitive *H. pylori* the eradication rates were 28% in the 3-day RAC, 90% in the 7-day RAC, 91% in the 10-day RAC, and 89% in the 10-day OAC groups. Eradication rates were much lower (20-30%) for the clarithromycin-resistant isolates.

A comparison of the Baseline and TOC visit *H. pylori* susceptibility results for clarithromycin is presented in TABLE 27. A follow-up endoscopy was performed and biopsy samples were obtained only in patients with a positive ¹³C-UBT at the post-treatment assessment to assess whether the organism had acquired resistance to the antibiotics used. The number of these patients with sensitive isolates at baseline was small, particularly in the 7-day RAC, 10-day RAC and OAC regimens (3, 6, and 2, respectively), and therefore, no meaningful conclusions can be drawn. A listing of the patient identification numbers and their *Helicobacter pylori* clarithromycin MIC values pre- and post-treatment are given in TABLE 28 for each of the four treatment groups. Eradication was not very good in the 3-day rabeprazole treatment group. In the other three treatment groups there were very few susceptible isolates that were not cured. It is, therefore, difficult to draw any conclusions on whether or not treatment causes an increase in clarithromycin MIC values. It appears from the data in the 3-day treatment group that treatment does not cause an increase in MIC values.

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TABLE 27
Comparison of Baseline and Test of Cure Visit *H. pylori*
Susceptibility to Clarithromycin

Treatment	Clarithromycin Sensitivity at Screening		
	Sensitive	Intermediate	Resistant
RAC 3-day –Test of Cure (N=47)			
Sensitive	42 (89%)	0	0
Intermediate	1 (2%)	0	0
Resistant	2 (4%)	0	2 (4%)
RAC 7-day –Test of Cure (N=10)			
Sensitive	2 (20%)	0	2 (20%)
Intermediate	0	0	1 (10%)
Resistant	1 (10%)	0	4 (40%)
RAC 10-day –Test of Cure (N=12)			
Sensitive	3 (25%)	0	0
Intermediate	1 (8%)	0	0
Resistant	2 (17%)	0	6 (50%)
OAC 10-day –Test of Cure (N=13)			
Sensitive	0	0	1 (8%)
Intermediate	0	0	0
Resistant	2 (15%)	0	10 (77%)
Total –Test of Cure (N=82)			
Sensitive	47 (57%)	0	3 (4%)
Intermediate	2 (2%)	0	1 (1%)
Resistant	7 (9%)	0	22 (27%)

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ACIPHEX® (rabeprazole sodium) for *H. pylori*TABLE 28--Patients with *H. pylori* Isolates with Clarithromycin MIC Values at Baseline and Test-of-Cure (TOC) Visits

Patient Number	Clarithromycin Susceptibility Results			
	Baseline MIC Value (µg/mL)	Baseline Susceptibility Status	TOC Visit MIC Value (µg/mL)	TOC Visit Susceptibility Status
RAC 3-day Treatment				
0587001534	≤0.008	Susceptible	0.12	Susceptible
0587001731	0.06	Susceptible	0.015	Susceptible
0588001255	0.015	Susceptible	0.03	Susceptible
0588001528	≤0.008	Susceptible	≤0.008	Susceptible
0589001559	≤0.008	Susceptible	0.015	Susceptible
0589002470	64	Resistant	64	Resistant
0590001010	0.06	Susceptible	0.06	Susceptible
0591001022	0.015	Susceptible	0.03	Susceptible
0593001267	≤0.008	Susceptible	0.03	Susceptible
0593001339	≤0.008	Susceptible	0.015	Susceptible
0593001665	0.03	Susceptible	≤0.008	Susceptible
0593002044	0.06	Susceptible	0.06	Susceptible
0594001261	0.06	Susceptible	0.015	Susceptible
0598001072	0.015	Susceptible	≤0.008	Susceptible
0598001592	0.015	Susceptible	0.015	Susceptible
0598002497	0.03	Susceptible	2	Resistant
0599001416	≤0.008	Susceptible	≤0.008	Susceptible
0599001734	0.015	Susceptible	≤0.008	Susceptible
0600001083	0.015	Susceptible	0.03	Susceptible
0601001512	0.03	Susceptible	0.5	Intermediate
0605001028	0.03	Susceptible	0.03	Susceptible
0605001277	0.12	Susceptible	0.12	Susceptible
0608001290	≤0.008	Susceptible	≤0.008	Susceptible
0608001345	0.06	Susceptible	0.03	Susceptible
0608002078	0.06	Susceptible	0.03	Susceptible
0610001051	0.015	Susceptible	0.03	Susceptible
0611001104	0.015	Susceptible	0.015	Susceptible
0611001165	0.03	Susceptible	0.06	Susceptible
0611001184	0.03	Susceptible	>256	Resistant
0611001504	0.03	Susceptible	0.03	Susceptible
0611001563	0.03	Susceptible	0.03	Susceptible
0611001566	0.12	Susceptible	0.015	Susceptible
0611001612	0.03	Susceptible	0.03	Susceptible
0611002468	≤0.008	Susceptible	≤0.008	Susceptible
0612001491	0.06	Susceptible	≤0.008	Susceptible
0613001062	≤0.008	Susceptible	0.06	Susceptible
0613001229	≤0.008	Susceptible	0.015	Susceptible
0614001540	≤0.008	Susceptible	≤0.008	Susceptible
0617001144	0.015	Susceptible	0.015	Susceptible
0617001381	≤0.008	Susceptible	0.015	Susceptible
0617001545	256	Resistant	8	Resistant
0617002072	≤0.008	Susceptible	≤0.008	Susceptible
0617002084	≤0.008	Susceptible	0.03	Susceptible
0618001402	0.03	Susceptible	≤0.008	Susceptible
0619001073	0.015	Susceptible	0.06	Susceptible
0620001123	≤0.008	Susceptible	≤0.008	Susceptible
0638001376	0.015	Susceptible	0.015	Susceptible

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ACIPHEX® (rabeprazole sodium) for *H. pylori*

TABLE 28 (Continued)
 Patients with *H. pylori* Isolates with Clarithromycin MIC Values
 at Baseline and Test-of-Cure (TOC) Visits

Patient Number	Clarithromycin Susceptibility Results			
	Baseline MIC Value ($\mu\text{g/mL}$)	Baseline Susceptibility Status	TOC Visit MIC Value ($\mu\text{g/mL}$)	TOC Visit Susceptibility Status
RAC 7-day Treatment				
0581001507	≤ 0.008	Susceptible	4	Resistant
0582001455	0.015	Susceptible	0.015	Susceptible
0583001085	2	Resistant	0.03	Susceptible
0588002087	8	Resistant	16	Resistant
0600001082	0.015	Susceptible	0.015	Susceptible
0604001458	32	Resistant	8	Resistant
0611001612	8	Resistant	128	Resistant
0613002157	32	Resistant	0.25	Susceptible
0614001538	64	Resistant	0.5	Intermediate
0638001375	4	Resistant	32	Resistant
RAC 10-day Treatment				
0582001454	8	Resistant	8	Resistant
0587001136	0.03	Susceptible	0.015	Susceptible
0589002469	16	Resistant	32	Resistant
0590001012	16	Resistant	64	Resistant
0591001687	0.25	Susceptible	0.5	Intermediate
0593001250	0.03	Susceptible	0.12	Susceptible
0594001262	0.06	Susceptible	8	Resistant
0597001670	≤ 0.008	Susceptible	8	Resistant
0608001291	≤ 0.008	Susceptible	0.06	Susceptible
0611001568	64	Resistant	256	Resistant
0611002465	32	Resistant	16	Resistant
0620001638	256	Resistant	128	Resistant
OAC 10-day Treatment				
0582001453	32	Resistant	0.03	Susceptible
0587001732	0.12	Susceptible	2	Resistant
0591001421	≤ 0.008	Susceptible	16	Resistant
0598001186	32	Resistant	8	Resistant
0608001706	1	Resistant	4	Resistant
0609001556	16	Resistant	16	Resistant
0611001564	16	Resistant	4	Resistant
0613001063	4	Resistant	8	Resistant
0616001030	>256	Resistant	>256	Resistant
0617001145	16	Resistant	16	Resistant
0617001542	16	Resistant	4	Resistant
0622001438	2	Resistant	4	Resistant
0662001605	64	Resistant	8	Resistant

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ACIPHEX® (rabeprazole sodium) for *H. pylori*

A total of 507 patients had *H. pylori* isolates that were considered to be susceptible to clarithromycin at Baseline (124 patients in the RAC 3-day group, 129 patients in the RAC 7-day group, 135 in the RAC 10-day group, and 119 patients in the OAC group). Of these 507 patients, 29 patients had isolates considered to be resistant to clarithromycin at the Test-of-Cure (TOC) visit (4 patients in the RAC 3-day group, 5 patients in the RAC 7-day group, 8 patients in the RAC 10-day group, and 12 patients in the OAC group), two patients had an isolate classified as intermediate for clarithromycin at the TOC visit, 47 patients had isolates that were still susceptible to clarithromycin. Three hundred forty-three (343) of the 507 patients with isolates that were susceptible to clarithromycin at baseline were considered cured and no isolates were, therefore, available for susceptibility testing at the TOC visit.

A comparison of the baseline *H. pylori* clarithromycin susceptibility status results and the *H. pylori* eradication status at the TOC visit is presented in TABLE 29 for the ITT population. In the ITT patients in whom eradication failed, 11 of 36 (31%) patients in the 7-day RAC group, 8 of 31 (26%) patients in the 10-day RAC group, and 13 of 38 (34%) patients in the OAC group were infected with *Helicobacter pylori* resistant to clarithromycin. In the 3-day RAC group 9 of 101 (9%) were infected with clarithromycin-resistant organisms.

TABLE 29
Summary of Shift in Clarithromycin Sensitivity by Eradication Rate—ITT Population

Treatment	Clarithromycin Pretreatment Results	Total Number	<i>H. pylori</i> Negative (Eradicated)	<i>H. pylori</i> Positive (Not Eradicated) Post-Treatment Susceptibility Results			
				Susceptible	Intermediate	Resistant	No MIC
RAC 3-day	Susceptible	124	33	42	1	2	46
	Intermediate	1	0	0	0	0	1
	Resistant	9	0	0	0	2	7
RAC 7-day	Susceptible	129	104	2	0	1	22
	Intermediate	0	0	0	0	0	0
	Resistant	16	5	2	1	4	4
RAC 10-day	Susceptible	135	112	3	1	2	17
	Intermediate	0	0	0	0	0	0
	Resistant	9	1	0	0	6	2
OAC 10-day	Susceptible	119	94	0	0	2	23
	Intermediate	1	1	0	0	0	0
	Resistant	17	4	1	0	10	2

Includes only patients with pretreatment and post-treatment clarithromycin susceptibility test results. Susceptibility (S) MIC \leq 0.25 μ g/mL, Intermediate (I) MIC = 0.5 μ g/mL, Resistant (R) MIC \geq 1.0 μ g/mL.

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ACIPHEX® (rabeprazole sodium) for *H. pylori*Summary of Clarithromycin Results (Study 604)

About 9% of the *Helicobacter pylori* isolates in clinical trial 604 were resistant to clarithromycin pre-treatment. The distribution of pre-treatment clarithromycin MIC values appears to be bimodal. One population had MIC values of ≤ 0.25 $\mu\text{g/mL}$ and the other population had MIC values of ≥ 8 $\mu\text{g/mL}$. A few isolates had MIC values between these two populations. Patients that had high clarithromycin MICs did not have their *Helicobacter pylori* eradicated as readily as those with isolates with low clarithromycin MIC values.

Treatment with rabeprazole plus clarithromycin and amoxicillin (RAC) for 3 days did not give a very good eradication rate for eliminating *H. pylori* (27%). Treatment with RAC for 7-days (77% eradication rate in the ITT population) and RAC for 10-days (78% eradication rate) gave results similar to those obtained with omeprazole plus clarithromycin and amoxicillin (OAC) which had an eradication rate in the ITT population of 73%.

None of the treatments in this study lead to an increase in resistance to clarithromycin.

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ACIPHEX® (rabeprazole sodium) for *H. pylori***AMOXICILLIN SUSCEPTIBILITY TEST RESULTS AND BACTERIOLOGICAL OUTCOMES**

Table 30 presents the distribution of the baseline amoxicillin MIC values by the *Helicobacter pylori* status at the Test-of-Cure (TOC) visit for all four treatment groups combined. There were only two baseline *H. pylori* isolates with a MIC value of at least 0.5 µg/mL. One of these two patients had *H. pylori* eradication at the TOC visit and the other did not have eradication.

TABLE 30
Distribution of Baseline Amoxicillin MIC Values for *H. pylori*
Based on Eradication Status at the TOC Visit (Number of Patients)
All Treatment Groups Combined

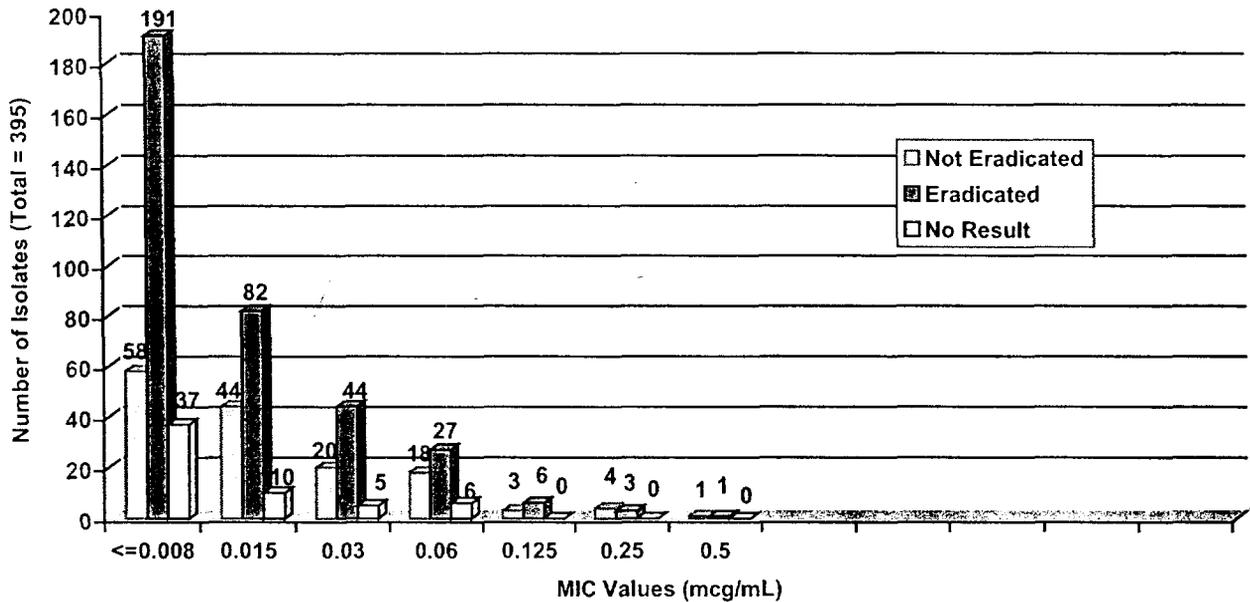
Baseline Amoxicillin MIC values (µg/mL)	TOC Visit <i>H. pylori</i> Status		
	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	No <i>H. pylori</i> Eradication Results
≤0.008	191 (66.8%)	58	37
0.015	82 (60.3%)	44	10
0.03	44 (63.8%)	20	5
0.06	27 (52.9%)	18	6
0.125	6 (66.6%)	3	0
0.25	3 (42.9%)	4	0
0.5	1 (50.0%)	1	0
Total	354 (62.2%)	148	58

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Figure 4 shows this data in a graphic format.

Figure 4
 Distribution of Baseline Amoxicillin MIC Values
 By *H. pylori* Eradication Status at the TOC visit
 All Treatment Groups



These data demonstrate that most *H. pylori* isolates are susceptible to amoxicillin. In rare instances an isolate that is not susceptible ($MIC \geq 0.5 \mu g/mL$) may be found. Eradication status at the TOC visit does not appear to be related to the amoxicillin MIC of the isolate at Baseline.

TABLE 31 shows the results by treatment group based on the baseline amoxicillin MIC value. This table shows that 3-day rabeprazole plus amoxicillin and clarithromycin treatment (3-day RAC) was not very good at eradicating *Helicobacter pylori*. RAC 7-day and RAC 10-day treatment was as effective as omeprazole plus clarithromycin and amoxicillin 10-day treatment in eradicating *H. pylori*. Eradication does not seem to be related to amoxicillin MIC values at baseline, this may be due to the fact that all isolates had low amoxicillin MIC values.

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TABLE 31
Distribution of Baseline Amoxicillin MIC values for *H. pylori* on Eradication Status at the TOC Visit
All Available Data by Treatment Group

Baseline Clarithromycin MIC values (µg/mL)	TOC Visit <i>H. pylori</i> Status											
	RAC 3-day			RAC 7-day			RAC 10-day			OAC 10-day		
	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing	<i>H. pylori</i> Eradicated	<i>H. pylori</i> Not Eradicated	Results Missing
≤0.008	17	35	8	63	7	11	58	9	5	53	7	13
0.015	8	30	4	23	3	2	30	3	3	21	8	1
0.03	4	11	0	13	4	1	15	2	2	12	3	2
0.06	3	7	2	5	5	2	9	4	1	10	2	1
0.125	1	3	0	2	0	0	0	0	0	3	0	0
0.25	0	1	0	1	1	0	2	1	0	0	1	0
0.5	0	0	0	1	1	0	0	0	0	0	0	0
Total	33 (24.6%)	87 (64.9%)	14 (10.4%)	108 (74.5%)	21 (14.5%)	16 (11.0%)	114 (79.2%)	19 (13.2%)	11 (7.6%)	99 (72.3%)	21 (15.3%)	17 (12.4%)

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A summary of *Helicobacter pylori* outcome by sensitivity to amoxicillin at screening in the ITT population is presented in TABLE 32, and a summary of *H. pylori* outcome by amoxicillin sensitivity at screening in the per-protocol (PP) population is presented in TABLE 33.

TABLE 32
Summary of *Helicobacter pylori* Outcome by Amoxicillin Sensitivity at Screening
Intent-to-Treat Patients (ITT) (Study 604)

Treatment	Outcome	
	Eradicated	Not Eradicated
RAC 3-day (N=134)		
Sensitive	33 (25%)	101 (75%)
Intermediate	0	0
Resistant	0	0
RAC 7-day (N=145)		
Sensitive	107 (75%)	36 (25%)
Intermediate	0	0
Resistant	1 (50%)	1 (50%)
RAC 10-day (N=144)		
Sensitive	114 (79%)	30 (21%)
Intermediate	0	0
Resistant	0	0
OAC 10-day (N=137)		
Sensitive	99 (72%)	38 (28%)
Intermediate	0	0
Resistant	0	0

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TABLE 33
Summary of *Helicobacter pylori* Outcome by Amoxicillin Sensitivity at Screening
Per Protocol (PP) Patients (Study 604)

Treatment	Outcome	
	Eradicated	Not Eradicated
RAC 3-day (N=121)		
Sensitive	32 (26%)	89 (74%)
Intermediate	0	0
Resistant	0	0
RAC 7-day (N=119)		
Sensitive	99 (85%)	18 (15%)
Intermediate	0	0
Resistant	1 (50%)	1 (50%)
RAC 10-day (N=125)		
Sensitive	107 (86%)	18 (14%)
Intermediate	0	0
Resistant	0	0
OAC 10-day (N=122)		
Sensitive	97 (80%)	23 (20%)
Intermediate	0	0
Resistant	0	0

These tables demonstrate that in the ITT patients with amoxicillin-sensitive *H. pylori*, the eradication rates were 25% in the 3-day RAC, 75% in the 7-day RAC, 79% in the 10-day RAC, and 72% in the 10-day OAC treatment groups. In the PP patients with amoxicillin-sensitive *H. pylori* the eradication rates were 26% in the 3-day RAC, 85% in the 7-day RAC, 86% in the 10-day RAC, and 80% in the 10-day OAC groups. There were only two isolates that were not sensitive to amoxicillin. The eradication rate for these two isolates was 50%.

A comparison of the Baseline and Test-of-Cure visit *H. pylori* susceptibility results for amoxicillin is presented in TABLE 34. A follow-up endoscopy was performed and biopsy samples were obtained only in patients with a positive ¹³C-UBT at the post-treatment assessment to assess whether the organism had acquired resistance to the antibiotics used. There were 46 of these patients in the 3-day RAC group, and 10 each in the other groups. All isolates were susceptible to amoxicillin both before and after treatment. Most pre- and post-treatment isolates had amoxicillin MIC values that were within one dilution of each other. A listing of the patient identification numbers and their *Helicobacter pylori* amoxicillin MIC values pre- and post-treatment are given in TABLE 35 for each of the four treatment groups. It appears from the data that treatment does not cause an increase in MIC values.

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TABLE 34
Comparison of Baseline and Test of Cure Visit *H. pylori*
Susceptibility to Amoxicillin

Treatment	Amoxicillin Sensitivity at Screening		
	Sensitive	Intermediate	Resistant
RAC 3-day –Test of Cure (N=46)			
Sensitive	46 (100%)	0	0
Intermediate	0	0	0
Resistant	0	0	0
RAC 7-day –Test of Cure (N=10)			
Sensitive	10 (100%)	0	0
Intermediate	0	0	0
Resistant	0	0	0
RAC 10-day –Test of Cure (N=10)			
Sensitive	10 (100%)	0	0
Intermediate	0	0	0
Resistant	0	0	0
OAC 10-day –Test of Cure (N=10)			
Sensitive	10 (100%)	0	0
Intermediate	0	0	0
Resistant	0	0	0
Total –Test of Cure (N=76)			
Sensitive	76 (100%)	0	0
Intermediate	0	0	0
Resistant	0	0	0

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TABLE 35--Patients with *H. pylori* Isolates with Amoxicillin MIC Values at Baseline and Test-of-Cure (TOC) Visits

Patient Number	Amoxicillin Susceptibility Results			
	Baseline MIC Value (µg/mL)	Baseline Susceptibility Status	TOC Visit MIC Value (µg/mL)	TOC Visit Susceptibility Status
RAC 3-day Treatment				
0587001133	≤0.008	Susceptible	0.015	Susceptible
0587001534	0.015	Susceptible	≤0.008	Susceptible
0587001731	0.015	Susceptible	0.25	Susceptible
0588001255	0.015	Susceptible	0.03	Susceptible
0388001528	≤0.008	Susceptible	≤0.008	Susceptible
0589001559	0.12	Susceptible	0.12	Susceptible
0589002470	0.015	Susceptible	0.015	Susceptible
0590001010	0.015	Susceptible	≤0.008	Susceptible
0591001022	≤0.008	Susceptible	≤0.008	Susceptible
0593001267	≤0.008	Susceptible	≤0.008	Susceptible
0593001339	≤0.008	Susceptible	0.015	Susceptible
0593001665	≤0.008	Susceptible	≤0.008	Susceptible
0593001757	≤0.008	Susceptible	0.015	Susceptible
0594001261	0.015	Susceptible	≤0.008	Susceptible
0598001072	0.015	Susceptible	≤0.008	Susceptible
0598001592	0.015	Susceptible	0.015	Susceptible
0598002497	0.015	Susceptible	≤0.008	Susceptible
0599001416	0.015	Susceptible	≤0.008	Susceptible
0599001734	0.03	Susceptible	0.03	Susceptible
0600001083	0.015	Susceptible	0.015	Susceptible
0601001512	≤0.008	Susceptible	≤0.008	Susceptible
0605001028	≤0.008	Susceptible	≤0.008	Susceptible
0605001277	0.015	Susceptible	≤0.008	Susceptible
0608001290	<0.008	Susceptible	0.03	Susceptible
0608001345	0.015	Susceptible	0.015	Susceptible
0608002078	≤0.008	Susceptible	0.03	Susceptible
0610001051	≤0.008	Susceptible	0.015	Susceptible
0611001104	0.03	Susceptible	0.015	Susceptible
0611001165	≤0.008	Susceptible	≤0.008	Susceptible
0611001184	≤0.008	Susceptible	0.015	Susceptible
0611001504	≤0.008	Susceptible	≤0.008	Susceptible
0611001563	0.015	Susceptible	0.015	Susceptible
0611001566	0.06	Susceptible	0.03	Susceptible
0611001612	0.03	Susceptible	0.06	Susceptible
0612001491	0.03	Susceptible	≤0.008	Susceptible
0613001062	≤0.008	Susceptible	≤0.008	Susceptible
0613001229	0.015	Susceptible	0.015	Susceptible
0614001540	≤0.008	Susceptible	≤0.008	Susceptible
0617001144	0.015	Susceptible	≤0.008	Susceptible
0617001381	≤0.008	Susceptible	0.015	Susceptible
0617001545	0.12	Susceptible	0.06	Susceptible
0617002072	0.12	Susceptible	0.25	Susceptible
0617002084	0.03	Susceptible	0.06	Susceptible
0618001402	≤0.008	Susceptible	≤0.008	Susceptible
0620001123	≤0.008	Susceptible	≤0.008	Susceptible
0638001376	0.015	Susceptible	0.015	Susceptible

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TABLE 35 (Continued)
 Patients with *H. pylori* Isolates with Amoxicillin MIC Values
 at Baseline and Test-of-Cure (TOC) Visits

Patient Number	Amoxicillin Susceptibility Results			
	Baseline MIC Value (µg/mL)	Baseline Susceptibility Status	TOC Visit MIC Value (µg/mL)	TOC Visit Susceptibility Status
RAC 7-day Treatment				
0581001507	0.06	Susceptible	0.12	Susceptible
0582001455	0.06	Susceptible	≤0.008	Susceptible
0583001085	0.015	Susceptible	≤0.008	Susceptible
0588002087	≤0.008	Susceptible	≤0.008	Susceptible
0600001082	≤0.008	Susceptible	≤0.008	Susceptible
0604001458	0.015	Susceptible	≤0.008	Susceptible
0611001582	0.03	Susceptible	0.015	Susceptible
0613002157	≤0.008	Susceptible	0.015	Susceptible
0614001538	0.06	Susceptible	0.03	Susceptible
0638001375	0.015	Susceptible	0.015	Susceptible
RAC 10-day Treatment				
0587001136	≤0.008	Susceptible	≤0.008	Susceptible
0589002469	0.06	Susceptible	0.12	Susceptible
0590001012	0.015	Susceptible	0.06	Susceptible
0591001687	≤0.008	Susceptible	≤0.008	Susceptible
0593001267	≤0.008	Susceptible	≤0.008	Susceptible
0597001670	≤0.008	Susceptible	0.06	Susceptible
0608001291	≤0.008	Susceptible	0.06	Susceptible
0611001568	0.06	Susceptible	0.03	Susceptible
0611002465	≤0.008	Susceptible	0.015	Susceptible
0620001638	0.06	Susceptible	0.06	Susceptible
OAC 10-day Treatment				
0582001453	0.03	Susceptible	0.03	Susceptible
0591001421	≤0.008	Susceptible	0.06	Susceptible
0598001186	0.015	Susceptible	≤0.008	Susceptible
0608001706	0.015	Susceptible	0.015	Susceptible
0609001556	≤0.008	Susceptible	0.25	Susceptible
0611001564	0.25	Susceptible	0.03	Susceptible
0613001063	0.015	Susceptible	0.015	Susceptible
0617001542	0.06	Susceptible	0.015	Susceptible
0622001438	≤0.008	Susceptible	≤0.008	Susceptible
0662001605	0.015	Susceptible	0.12	Susceptible

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ACIPHEX® (rabeprazole sodium) for *H. pylori*

A total of 558 patients had *H. pylori* isolates that were considered to be susceptible to amoxicillin at Baseline (134 patients in the RAC 3-day group, 143 patients in the RAC 7-day group, 144 in the RAC 10-day group, and 137 patients in the OAC group). Of these 558 patients, no patients had isolates considered to be resistant to amoxicillin at the Test-of-Cure (TOC) visit, no patients had an isolate classified as intermediate for amoxicillin at the TOC visit, 76 patients had isolates that were still susceptible to clarithromycin. Three hundred fifty-three (353) of the 558 patients with isolates that were susceptible to amoxicillin at baseline were considered cured and no isolates were, therefore, available for susceptibility testing at the TOC visit.

A comparison of the baseline *H. pylori* amoxicillin susceptibility status results and the *H. pylori* eradication status at the TOC visit is presented in TABLE 36 for the ITT population. All but two of the isolates were susceptible. None of the susceptible isolates became resistant after treatment.

TABLE 36
Summary of Shift in Amoxicillin Sensitivity by Eradication Rate—ITT Population

Treatment	Amoxicillin Pretreatment Results	Total Number	<i>H. pylori</i> Negative (Eradicated)	<i>H. pylori</i> Positive (Not Eradicated) Post-Treatment Susceptibility Results			
				Susceptible	Intermediate	Resistant	No MIC
RAC 3-day	Susceptible	134	33	46	0	0	55
	Intermediate	0	0	0	0	0	0
	Resistant	0	0	0	0	0	0
RAC 7-day	Susceptible	143	107	10	0	0	26
	Intermediate	0	0	0	0	0	0
	Resistant	2	1	0	0	0	1
RAC 10-day	Susceptible	144	114	10	0	0	20
	Intermediate	0	0	0	0	0	0
	Resistant	0	0	0	0	0	0
OAC 10-day	Susceptible	137	99	10	0	2	28
	Intermediate	0	0	0	0	0	0
	Resistant	0	0	0	0	0	0

Includes only patients with pretreatment and post-treatment amoxicillin susceptibility test results. Susceptibility (S) MIC \leq 0.25 μ g/mL, Resistant (R) MIC \geq 0.5 μ g/mL.

Summary of Amoxicillin Results

Only two *Helicobacter pylori* isolates in the clinical trial were not susceptible (MIC \geq 0.5 μ g/mL) to amoxicillin pre-treatment. Eradication of *H. pylori* did not appear to be related to amoxicillin MIC value.

Treatment with RAC for 3-days did not give a very good *H. pylori* eradication rate (25%). Treatment with RAC for 7-days (75% eradication rate), RAC for 10-days (79% eradication rate) or OAC for 10-days (72% eradication rate) appeared to be equivalent.

Treatment did not lead to the development of amoxicillin-resistant *H. pylori*. All post-treatment isolates were still susceptible to amoxicillin.

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ACIPHEX® (rabeprazole sodium) for *H. pylori*

LABELING

The label that has been submitted follows the outline used for other recently approved proton-pump inhibitor plus clarithromycin and amoxicillin labels in the microbiology subsection.

The last statement in the microbiology subsection that reads

must be deleted. No standard method has been developed for the *in vitro* testing of rabeprazole. Therefore, the meaning of these MIC values is unknown. It has also been shown that rabeprazole alone does not eradicate *H. pylori* very well. The testing of only 15 isolates also would not be enough to get an organism listed in the label even if a standard method had been developed. The actual MIC values are also not usually allowed in labels.

Helicobacter pylori should be written out in full instead of *H. pylori* where indicated. Other minor changes to the proposed label are indicated in the recommendations to the sponsor on pages 57-59.

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ON ORIGINAL

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3 page(s) of
revised draft labeling
has been redacted
from this portion of
the review.

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Peter A. Dionne
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CONCURRENCES:

HFD-590/Div Dir _____ Signature _____ Date _____
HFD-590/TLMicro _____ Signature _____ Date _____

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HFD-590/Original NDA # 21-456
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HFD-590/Micro/PDionne
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HFD-590/Chem/GHolbert
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Peter Dionne
6/26/02 01:58:44 PM
MICROBIOLOGIST

Shukal signed 6/15/02; Ken signed 6/26/02

Shukal Bala
6/30/02 05:20:24 PM
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