

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:20406/S021

MICROBIOLOGY REVIEW(S)

FEB 12 1998

Case
Webster

CONSULT MICROBIOLOGY REVIEW TO HFD-180
DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
DIVISION OF SPECIAL PATHOGENS AND IMMUNOLOGIC DRUG PRODUCTS
(HFD-590)

NDA # 20-406, S021

REVIEWER: Linda J. Utrup, Ph.D.

CORRESPONDENCE DATE: 25 JUNE 1997

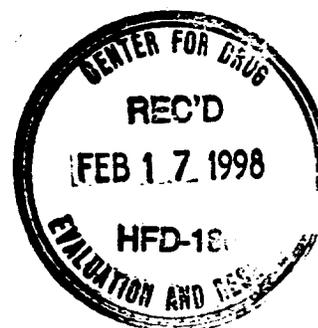
CDER RECEIPT DATE: 1 AUG 1997

REVIEW ASSIGN DATE:

REVIEW COMPLETE DATE: 16 DEC 1997

APPEARS THIS WAY
ON ORIGINAL

SPONSOR: TAP HOLDINGS INC.
2355 Waukegan Rd.
Deerfield, IL 60015



SUBMISSIONS REVIEWED: Supplement 021

DRUG CATEGORY: *Helicobacter pylori* eradication

INDICATION: *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence.

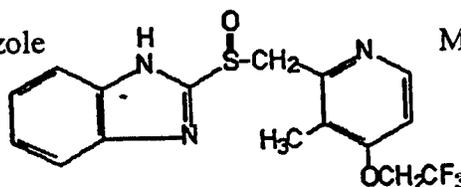
DOSAGE FORMS: Tablets

PRODUCT NAMES:

APPEARS THIS WAY
ON ORIGINAL

1. a. PROPRIETARY: PREVACID
- b. NONPROPRIETARY: LANSOPRAZOLE
- c. CHEMICAL: 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl]methyl]sulfinyl]benzimidazole
2. a. PROPRIETARY: BIAXIN
- b. NONPROPRIETARY: CLARITHROMYCIN
3. a. NONPROPRIETARY: AMOXICILLIN

STRUCTURAL FORMULA: lansoprazole



MW = 369.37

SUPPORTING DOCUMENTS

NDA 20-876: Lansoprazole/clarithromycin/amoxicillin
NDA 20-877: Lansoprazole/amoxicillin

NDA 20-406: Lansoprazole
NDA 50-662: Clarithromycin
IND
IND
IND
IND
IND

BACKGROUND:

The sponsor currently has approval for *H. pylori* eradication and reduction of the risk of duodenal ulcer recurrence for patients on a 14 day triple therapy regimen (30 mg lansoprazole BID, 1 gram amoxicillin BID, and 500 mg clarithromycin BID). They are currently seeking approval for a 10 day regimen with the same twice daily dosing of lansoprazole, amoxicillin, and clarithromycin (triple therapy) as listed above. The indication sought is *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence. The sponsor wishes to establish that the 10 day triple therapy regimen was equivalent to the 14 day triple therapy regimen in eradicating *H. pylori*. The Medical Officer per protocol efficacy rates are 84% and 85% for 10 day and 14 day regimens respectively. The MITT rates are 81% and 82% for the 10 day and 14 day regimens respectively. The sponsor also claims that shortening the course of therapy does not impact on the development of antibiotic resistance. (Sponsor statement: Among the patients who were susceptible to clarithromycin or amoxicillin pretreatment and did not have their *H. pylori* eradicated posttreatment, none of the patients who had susceptibility results available posttreatment developed resistance to clarithromycin or had isolates of undefined susceptibility to amoxicillin.)

A single, multicenter pivotal clinical study (M95-399) was conducted to evaluate the efficacy and safety of the 10 day and 14 day triple therapy regimens in 284 patients. Pretreatment infection and post-treatment eradication of *H. pylori* were determined by means of multiple testing procedures, histology, culture and the rapid urease test.

Microbiology Reviewer Comments: There was one patient on the 10 day therapy regimen who had emerging clarithromycin resistance when tested by the

agar dilution methodology. Further reviewer comments are given after the presentation of the results.

APPEARS THIS WAY
ON ORIGINAL

Mechanism of Action

There is evidence that lansoprazole exhibits some inhibitory effect on *H. pylori*. The MIC₅₀ and MIC₉₀ of lansoprazole as determined by the agar dilution method is 6.25 µg/mL, which is four-fold more potent than another proton pump inhibitor, omeprazole, and comparable to bismuth citrate.¹ In addition, two acid metabolites of lansoprazole, AG-2000 and AG-1812, are two- to four-fold more active than the parent compound. It has been proposed that lansoprazole is readily converted into these metabolites within the acidic compartment of gastric parietal cells.² In the clinical program, lansoprazole monotherapy exhibited negligible effect on eradication of *H. pylori*.

Several studies have demonstrated that clarithromycin exhibits good *in vitro* activity against *H. pylori*.³⁻⁵ The MIC of clarithromycin for *H. pylori* isolates ranges from 0.03 µg/mL to 0.06 µg/mL.³⁻⁴ The 14-hydroxy metabolite of clarithromycin also exhibits potent activity against *H. pylori* (MIC₉₀=0.06 µg/mL),^{3,5} and the effect of the combination of clarithromycin and its 14-hydroxy metabolite has been reported to be additive.⁵

Studies have also determined that the *in vitro* activity of clarithromycin is affected by acid pH.³⁻⁵ Clarithromycin is less active at pH below 6.5, but remains the most active of the macrolides tested in an environment of lower pH.³⁻⁵ Clarithromycin is extremely active exhibits little change in activity over this pH range. In contrast, other macrolides show a substantial decrease in activity as pH decreases from pH 8.0 to pH 6.5.

Amoxicillin/ampicillin exhibit *in vitro* activity against *H. pylori*. Ampicillin was used in these clinical studies as a substitute for amoxicillin for testing in the laboratory. Ampicillin is 10-fold more active at neutral pH than at the more acidic pH values.⁶ The reduction in intraluminal H⁺ activity will increase the pH at the surface of the epithelial cell, possibly to alkaline levels. The prolonged elevation of intragastric pH increases the concentration of such acid-labile antibiotics in gastric juice and may also prolong their effectiveness.⁷

Clarithromycin has been shown to have potent bactericidal activity against *H. pylori*.^{5,8-9} Clarithromycin exerts its antimicrobial effect by binding to a conserved loop in 23S rRNA within the 50S ribosomal subunit and inhibiting translation.¹⁰ Clarithromycin and 14-hydroxy clarithromycin kill both non-growing and slow-growing organisms, compared with ampicillin or metronidazole. At concentrations of only 0.12 µg/mL, clarithromycin reduces

culture viability by $3 \log_{10}$ CFU/mL within two to eight hours of culture, compared to little or no reduction by ampicillin, metronidazole, bismuth subcitrate in this time frame. Killing by clarithromycin is dose-dependent, but always exhibits growth-independence.⁸ Ampicillin and metronidazole began to exhibit killing activity only after the lag-phase, at least eight hours after initiation of culture, and do not reach the same magnitude of killing as clarithromycin until at least four to 12 hours later (12 to 20 hours after initiation of culture). Killing by ampicillin and metronidazole is also dose-dependent but remains growth-dependent.¹¹ It also has been demonstrated that rapid clarithromycin killing is observed during the growth phase of culture when drug is added near the end of lag-phase, indicating that killing occurs in both actively growing and stationary cells.⁸

Additionally, clarithromycin exhibits a long residence time on the ribosome. It has been suggested that, compared to other protein synthesis inhibitors, the prolonged interaction of clarithromycin with *H. pylori* ribosomes might explain its ability to kill the organism by increasing the efficiency of inhibition of protein synthesis.¹²

Lansoprazole lowers the intragastric pH, increasing the effectiveness of the antimicrobials which have decreased activity at lower pH.

Mechanism of Resistance - Clarithromycin

APPEARS THIS WAY ON ORIGINAL

Resistance of *H. pylori* to clarithromycin has been reported in several studies. *H. pylori* resistance to clarithromycin pretreatment has been reported in less than 10% of isolates.⁴ Several investigators reported isolation of clarithromycin-resistant *H. pylori* of patients after receiving clarithromycin as a single antibacterial agent.¹³⁻¹⁵ Another study reported that 12% of patients were infected with clarithromycin-resistant organisms pretreatment, and that resistant strains were isolated from 21% of the patients after treatment with clarithromycin alone.¹⁵

Acquisition of the clarithromycin-resistant phenotype in *H. pylori* can occur by a point mutation in one 23S rRNA gene. A study of this mechanism of resistance demonstrated A ↔ G transition mutations in a conserved loop within domain V of 23S rRNA. Two different A ↔ G transition mutations at positions similar to that of *E. coli* 23S rRNA positions 2058 or 2059 in the conserved domain V have been identified. Of 12 mutations identified, 10 were A2059G (the predominant mutation) and two were A2058G. Point mutations in 23S rRNA may alter the ribosomal target of clarithromycin and inhibit its interaction with *H. pylori* ribosomes thus maintaining viability of *H. pylori* mutant clones.¹⁰

Until recently, there were no published reports of amoxicillin-resistant *H. pylori* isolates. Recently, it has been suggested that subculturing the *H. pylori* on media containing amoxicillin has resulted in obtaining amoxicillin MIC of > 256 mcg/mL. Further testing is need to further explore this tolerance phenomenon.

APPEARS THIS WAY
ON ORIGINAL

Animal Models

Few animal models are adequate for *H. pylori* gastrointestinal infection. *H. pylori* infections have been established in gnotobiotic piglets¹⁶ and germ free rats¹⁷; however, these species do not develop ulcers. Ferrets are known to develop gastritis and ulcers as a natural disease, apparently related to *H. mustelae*.¹⁸ The obvious limitation of the ferret model is that *H. pylori* is not the organism involved, and thus the relevance to human disease is unclear.

METHODOLOGIES USED IN M95-399

APPEARS THIS WAY
ON ORIGINAL

Culture

Two gastric biopsy specimens (one from the greater curvature of the antrum and one from the corpus) were taken for culture at the screening and Week 6 visits. The specimens were placed in individual vials containing Stuart's transport media (without charcoal) and refrigerated at 2 to 8°C. The specimens shipped in a styrofoam box with two frozen ice packs (one above and one below the specimen bag) to The specimens were inoculated onto tryptic soy agar with 5% sheep blood and onto Skirrow's campy agar and incubated at 37°C in microaerobic conditions. *H. pylori* was identified by colony and Gram stain morphology and the production of catalase, oxidase, and urease. The isolates were stored at -70°C in tryptic soy broth with 15% glycerol and 50% laked horse blood. The technologists were unaware of the clinical status and the results of other *H. pylori* tests.

APPEARS THIS WAY
ON ORIGINAL

Susceptibility Assessment

Susceptibility tests were performed on biopsy specimens collected at the screening and Week 6 study visits using the E-test[®] () and agar dilution MIC. The antibiotics tested were ampicillin 0.016-256 mcg/mL, clarithromycin 0.016 - 256 mcg/mL, and metronidazole 0.002-32 mcg/mL. When more than one isolate was obtained form a patient at any time point, only a single isolate with the highest MIC was used in the susceptibility analysis.

The media used for the Etest methodology was Mueller-Hinton agar with 5% sheep blood. The sponsor states that an inoculum equivalent to a No. 1 MacFarland standard (9 to 12×10^8 cfu/mL) was used and the plates were taped using a gas permeable tape and incubated for 5 days under microaerobic conditions. The quality control organisms used by the sponsor for the Etest methodology were *Staphylococcus aureus* ATCC 29213 for ampicillin and clarithromycin and *Bacteroides fragilis* ATCC 25285 for metronidazole. The Etest gives intermediate values which fall in between the NCCLS interpretive standards and must be interpreted as the nearest higher two-fold dilution prior to placement into a susceptible, intermediate or resistant categories.

The sponsor's proposed susceptibility testing breakpoints based on the Etest data are listed in Table 1.

Antibiotic	Susceptible ($\mu\text{g/mL}$)	Intermediate ($\mu\text{g/mL}$)	Resistant ($\mu\text{g/mL}$)	Not Defined ($\mu\text{g/mL}$)
Amoxicillin ^a	≤ 0.25	N/A	N/A	> 0.25
Clarithromycin	≤ 0.5	$> 0.5 - \leq 2.0$	> 2	N/A

^a Ampicillin was used for testing.

Metronidazole was not a compound studied in the clinical program and the sponsor did not propose metronidazole breakpoints using the E-test methodology. The susceptibility breakpoints the sponsor used for metronidazole are susceptible $< 8 \mu\text{g/mL}$; resistant $\geq 8 \mu\text{g/mL}$.

Agar Dilution

Susceptibility results based on the agar dilution method were also collected in Study M95-399. The concentrations tested were amoxicillin 0.015 - 256 mcg/mL, clarithromycin 0.015 - 256 mcg/mL, and metronidazole 0.015 - 32 mcg/mL. Mueller Hinton agar with 5% defibrinated sheep blood was used. An inoculum equivalent to a No. 1 MacFarland standard (3×10^8 cfu/mL) was used and the plates were taped using a gas permeable tape and incubated for 5 days under microaerobic conditions. The quality control organisms used by the sponsor for the Etest methodology were *Staphylococcus aureus* ATCC 29213 (ampicillin and clarithromycin) and *Bacteroides fragilis* ATCC 25285 (metronidazole).

Microbiology Reviewer Comments

The agar dilution susceptibility testing methodology is the preferred susceptibility testing methodology when testing *H. pylori*. This is the recommendation of the *Helicobacter pylori* Susceptibility Testing Standardization Study Group of the National Committee of Clinical Laboratory Standards (NCCLS) and the FDA as stated in the Evaluability Criteria Document.

The reference microbiology laboratory's performance of the agar dilution and Etest methodology should be modified. Amoxicillin should be used instead of ampicillin when performing susceptibility tests because it is the actual agent given to the patient. The sponsor used amoxicillin when doing agar dilution testing, but used ampicillin for the Etest methodology. The upper range of the metronidazole concentrations tested should be expanded to >256 mcg/mL (for both Etest and agar dilution).

Inoculum suspensions having a turbidity equivalent to a No. 2 McFarland standard should be used. The sponsor stated that a No. 1 McFarland standard contained differing concentrations of organisms, Etest (9 to 12×10^8 cfu/mL) and for agar dilution (3×10^8 cfu/mL). A No. 1 McFarland standard should contain the same number of *H. pylori* colony forming units regardless of which testing methodology is used. Also, no colony counts of the *H. pylori* inoculum were included in the submission. Based on data from the *H. pylori* Susceptibility Testing Standardization Study Group, the colony counts for an *H. pylori* suspension equal to No. 2 McFarland are . The colony counts for an *H. pylori* suspension equivalent to a No. 1 McFarland should have lower colony counts, not higher as the sponsor indicates.

Taping of the Mueller-Hinton agar plates should not be done as it could interfere with the attainment of the microaerobic environment. Incubation should be 3 days in a microaerobic environment produced by a gas generating system. *H. pylori* quality control strain ATCC 43504 should be used. The quality control ranges should be , for amoxicillin and clarithromycin and for metronidazole. The sponsor made some deviations from the conventional rounding scheme in the original submission and this was not corrected even though it was requested in the July 24, 1997 letter the Agency sent to the company.

Microbiology Reviewer Breakpoints

Microbiology Reviewer Breakpoints for the agar dilution methodology are shown in Table 2.

Table 2. Microbiology Reviewer Agar Dilution Susceptibility Breakpoints for Amoxicillin and Clarithromycin

Antimicrobial	Susceptible (mcg/mL)	Intermediate (mcg/mL)	Resistant (mcg.mL)
Amoxicillin	≤ 0.25		
Clarithromycin	≤ 0.25	0.5 - 1.0	≥ 2.0

Additional information on the selection of these breakpoints will be included after the clinical results section.

Laboratory Success at Obtaining Susceptibility Testing Results

The laboratory, obtained susceptibility test results on less than 50 % of the *H. pylori* isolated. Table 3 contains the percentage of pretreatment and posttreatment isolates that had susceptibility test results when there was a positive culture, i.e. *H. pylori* was isolated.

Table 3. Isolates with Clarithromycin Susceptibility Test Results

	Pretreatment percent (n/N)	Posttreatment percent (n/N)
Culture positive isolates with:		
Agar dilution results	46 (150/329)	38 (13/34)
Etest results	52 (170/329)	44 (15/34)
Agar dilution and Etest results	42 (139/329)	38 (13/34)

Isolates with Amoxicillin (Ampicillin) Susceptibility Test Results

	PreTreatment percent (n/N)	Posttreatment percent (n/N)
Culture positive isolates with:		
Agar dilution results	43 (141/329)	35 (12/34)
Etest results	52 (171/329)	47 (16/34)
Agar dilution and Etest results	39 (127/329)	35 (12/34)

There were a number of patients who failed therapy, but posttreatment susceptibility results were not obtained. It is critical to include this concept when presenting emerging resistance data. A number of patients had missing pretreatment MIC values and these patients were not included in the analysis in the remainder of this review. Additionally, it should also be noted that the laboratory had some problems isolating *H. pylori* when other tests such as urease and histology would indicate that *H. pylori* was present.

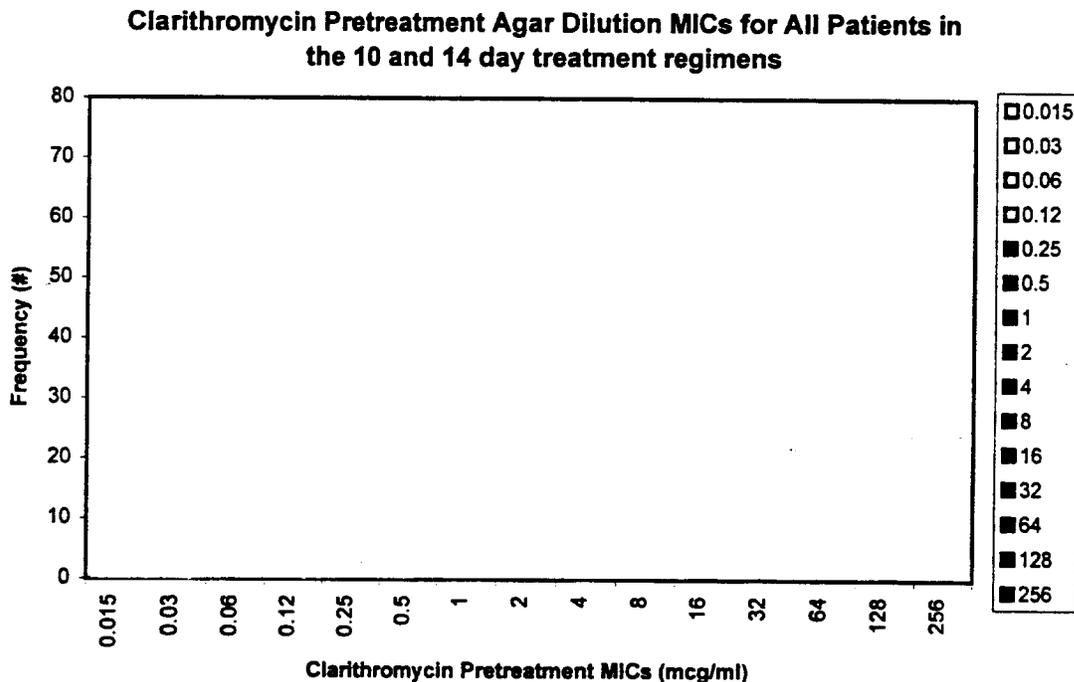
PRETREATMENT CLARITHROMYCIN SUSCEPTIBILITY TESTING RESULTS

APPEARS THIS WAY
ON ORIGINAL

Pretreatment susceptibility results for clarithromycin, amoxicillin (ampicillin used for Etest) and metronidazole were determined by agar dilution and Etest methodologies. Figure 1 is the presentation of the clarithromycin pretreatment MIC results from all patients that entered in the study regardless of which therapy regimen they were assigned as determined by the agar dilution methodology.

Figure 1

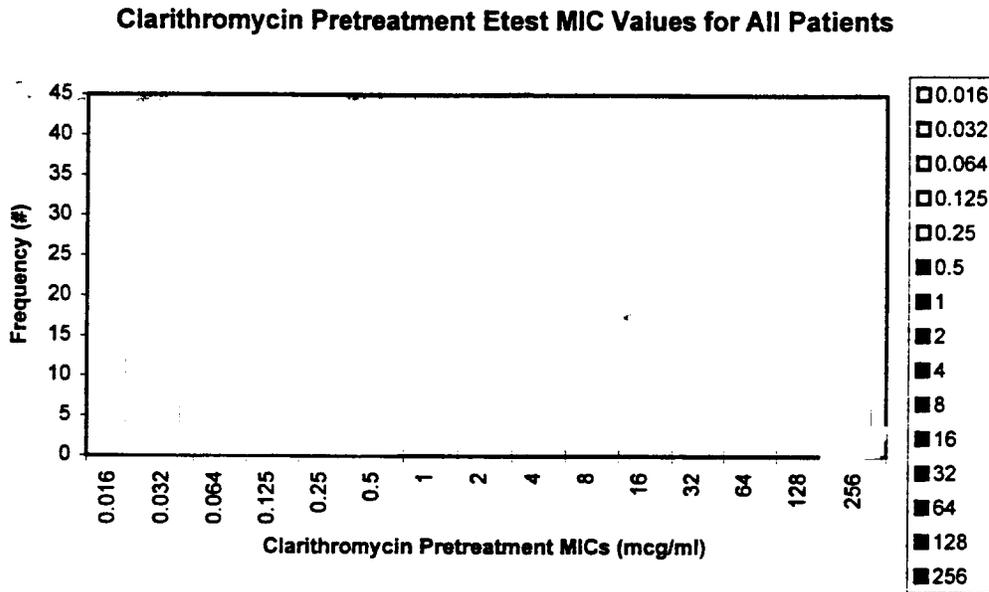
APPEARS THIS WAY
ON ORIGINAL



Using the agar dilution methodology, 11.3% (12/106) of all the patients with pretreatment clarithromycin results had MICs ≥ 2 mcg/mL and were resistant, 88.7% (94/106) had MICs of ≤ 0.25 mcg/mL and were susceptible.

Figure 2 is the presentation of the clarithromycin pretreatment MIC results from all patients that entered in the study regardless of which therapy regimen they were assigned as determined by the Etest methodology.

Figure 2.



Using the Etest methodology, 13.7% (17/124) of all the patients with pretreatment clarithromycin results had MICs ≥ 2 mcg/mL and were resistant, 85.5% (106/124) had MICs of ≤ 0.25 mcg/mL and were susceptible. One patient, 0.8% (1/124) had an intermediate clarithromycin MIC.

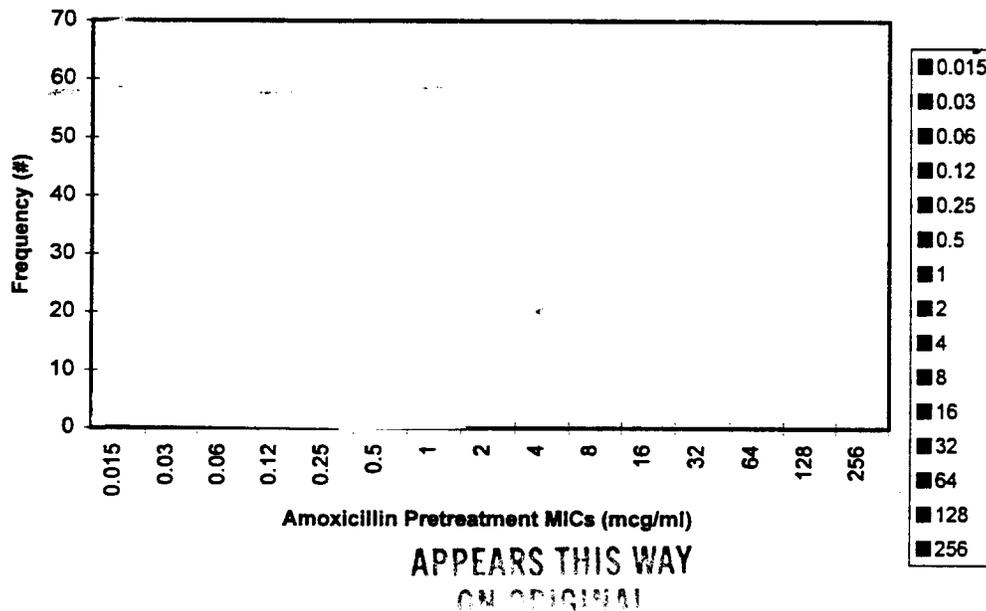
Figure 3 is the presentation of the amoxicillin pretreatment MIC results from all patients that entered in the study regardless of which therapy regimen they were assigned as determined by the agar dilution methodology.

APPEARS THIS WAY
ON ORIGINAL

Figure 3.

AMOXICILLIN PRETREATMENT SUSCEPTIBILITY TESTING RESULTS

Amoxicillin Pretreatment Agar Dilution MIC Values for All Patients in the 10 and 14 Day Triple Therapy Regimens



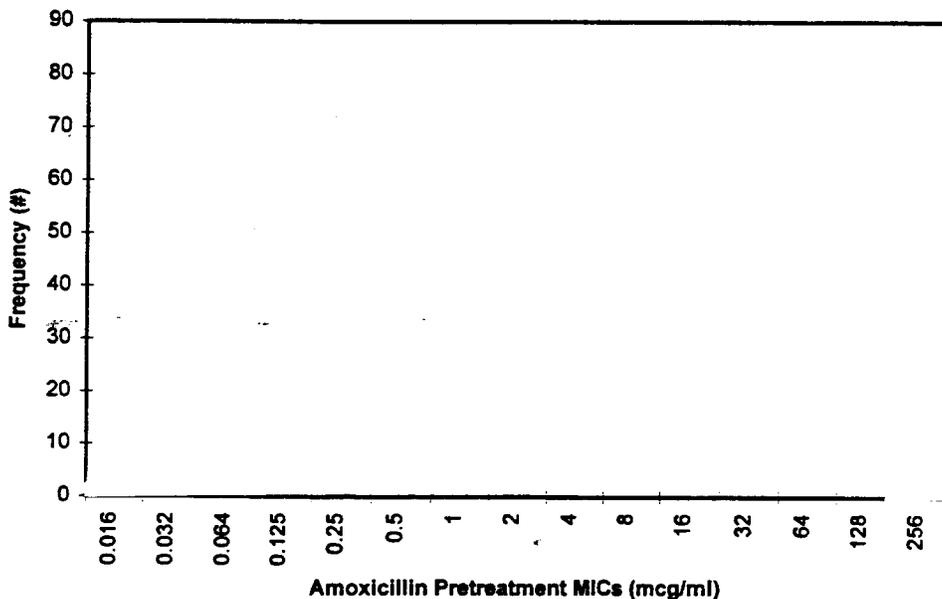
Using the agar dilution methodology, 98% (98/100) patients had amoxicillin pretreatment MICs of ≤ 0.25 mcg/mL. One patient had an MIC of 0.5 and another had an MIC of 1.0 mcg/mL.

Figure 4 is the presentation of the amoxicillin pretreatment MIC results from all patients that entered in the study regardless of which therapy regimen they were assigned as determined by the Etest methodology.

APPEARS THIS WAY ON ORIGINAL

Figure 4.

Amoxicillin Pretreatment Etest MIC Values for All Patients



Using the Etest methodology, 98.4% (122/124) patients had amoxicillin pretreatment MICs of ≤ 0.25 . Two patients had MICs of 2 and ≥ 256 respectively. Unfortunately, the patient with an amoxicillin MICs of ≥ 256 was not tested by the agar dilution methodology and failed to grow for the repeat E-test and therefore the results were not confirmed.

**APPEARS THIS WAY
ON ORIGINAL**

According to the sponsor, the clarithromycin, ampicillin and metronidazole MIC₅₀s, MIC₉₀s, and ranges for the pretreatment isolates as performed by Etest are shown in Table 4. (See microbiology reviewer comments)

Table 4.				
<i>In vitro</i> Clarithromycin, Amoxicillin, and Metronidazole MIC of Pretreatment <i>H. pylori</i> Isolates in Study M95-399				
Study Drug	Number of Isolates	MIC (µg/mL)		
		Range	50%	90%
Clarithromycin	124		0.032	256 ^a
Amoxicillin	124		0.016	0.047
Metronidazole	121		32	32

^a 14% of the isolates had MIC of ≥ 2.0 µg/mL.
^b The E-test was applied to the isolate with an amoxicillin MIC of >256 µg/mL a second time; however, the organism failed to grow.

Among the patients with pretreatment *H. pylori* isolates by culture and with susceptibility data available, 86% (107/124) were susceptible to clarithromycin, 98% (122/124) were susceptible to amoxicillin, and 26% (32/121) were susceptible to metronidazole. Two isolates had amoxicillin MICs of >256.00 µg/mL and 2.00 µg/mL, respectively. When the E-test was applied to the isolate with an amoxicillin MIC of >256 µg/mL a second time, the organism failed to grow.

Microbiology Reviewer Comments: The MIC₉₀ for clarithromycin by Etest is 256 mcg/mL and actually 86% (107/124) of the pretreatment isolates are susceptible. While this is a lower rate than 90%, clarithromycin is one of the more effective agents against *H. pylori*. The MIC₉₀ for clarithromycin by agar dilution would be 8 µg/mL, which is still be in the resistant range. These data indicate the need for performing pretreatment susceptibility testing, as the majority of patients with pretreatment clarithromycin resistant isolates will fail therapy.

Metronidazole Pretreatment MICs by the Etest methodology are shown in Table 5. While metronidazole wasn't given as part of any treatment regimen, it is interesting to examine the metronidazole pretreatment MICs of *H. pylori*.

Table 5.

SUMMARY OF MIC DISTRIBUTION PRETREATMENT METRONIDAZOLE SUSCEPTIBILITY

CUMULATIVE PERCENT	STUDIES	MIC	NUMBER OF ISOLATES
0.8	M95-399	0.19	1
1.7		0.25	1
3.3		0.50	2
7.4		1	5
9.9		1.5	3
14.9		2	6
16.5		3	2
22.3		4	7
26.4		6	5
34.7		8	10
38.8		12	5
43.8		16	6
100.0		32	68
		Total	121

Metronidazole breakpoints have not been established for *H. pylori*. If the metronidazole resistance breakpoint was ≥ 32 mcg/mL, 56% (68/121) of the isolates would be resistant. If the metronidazole resistance breakpoint was ≥ 16 mcg/mL, 65% (79/121) of the isolates would be resistant. If the metronidazole resistance breakpoint was ≥ 8 mcg/mL, 74% (89/121) of the isolates would be resistant. These numbers indicate high metronidazole pretreatment resistance rates.

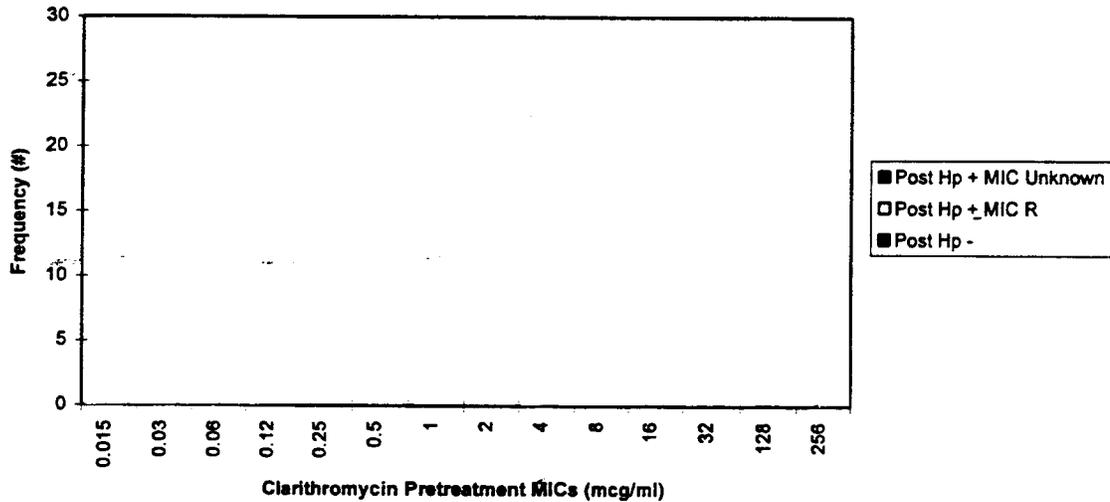
CLARITHROMYCIN SUSCEPTIBILITY TEST RESULTS AND BACTERIOLOGICAL/CLINICAL OUTCOMES

Clinical outcomes in *H. pylori* clinical trials is actually a bacteriological outcome with the presence or absence of the organism determining the clinical efficacy rates. Figure 5 is the presentation of the clarithromycin pretreatment agar dilution MIC results and bacteriological outcome for patients on the 14 day triple therapy regimen.

BEST POSSIBLE COPY

Figure 5.

Clarithromycin Pretreatment Agar Dilution MIC Values and Bacteriological/Clinical Outcomes for Patients on 14 Day Triple Therapy



The chart presentation of the above data is shown in Table 6.

Table 6. Clarithromycin Agar Dilution Results for 48 Patients Treated with the 14 Day Triple Therapy Regimen^a

Bacteriological and Clinical Responses

Pretreatment	Posttreatment			
	<i>H. pylori</i> negative (eradicated)	<i>H. pylori</i> positive (not eradicated)		
		Posttreatment susceptibility results ^b		
		S	I	R
				No MIC
Susceptible ^b 40	37			3
Intermediate ^b				
Resistant ^b 8	4		2	2

^a48 Patients had pretreatment MIC values and eradication status at 6 weeks post-treatment

^bSusceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC 0.5 - 1.0 mcg/mL, Resistant (R) MIC ≥ 2 mcg/mL

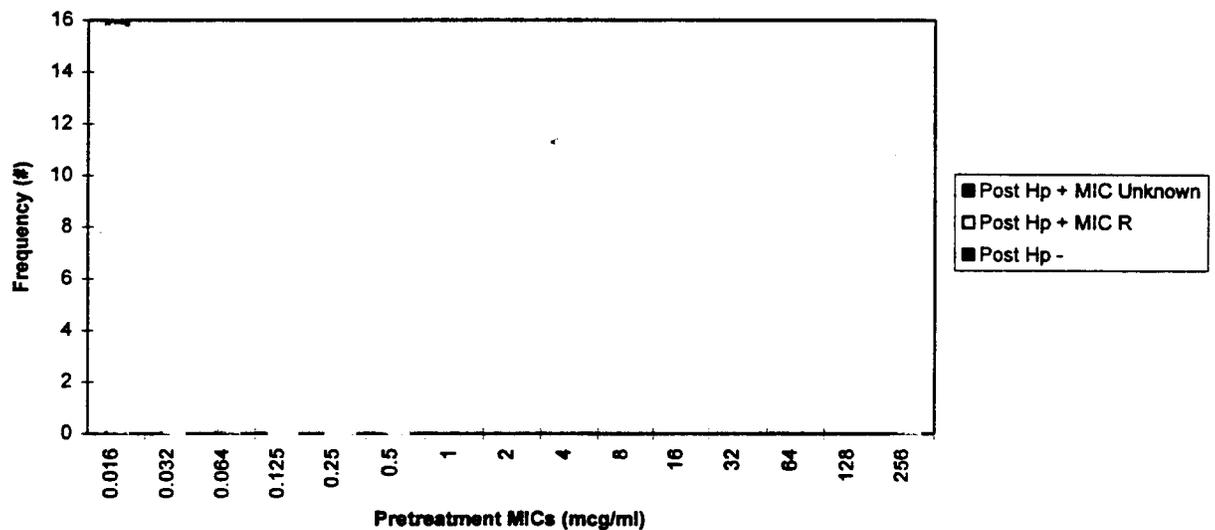
Eradication of *H. pylori* occurred in 37 of the 40 patients with clarithromycin susceptible *H. pylori* isolates and in 4 of the 8 patients with clarithromycin resistant isolates. Posttreatment MICs were not available for 5 of the 7 patients who failed 14 day triple therapy. The other two patients that failed therapy had clarithromycin resistant pre and posttreatment MICs.

Figure 6 is the presentation of the clarithromycin pretreatment Estest MIC results and clinical outcomes for patients on the 14 day triple therapy regimen.

Figure 6.

APPEARS THIS WAY
ON ORIGINAL

Clarithromycin Pretreatment Estest MIC Values and Bacteriological/Clinical Outcomes for Patients on 14 Day Triple Therapy



The data corresponding to Figure 6 is presented in Table 7.

APPEARS THIS WAY
ON ORIGINAL

Table 7. Clarithromycin Etest Results for 56 Patients Treated with the 14 Day Triple Therapy Regimen^a

Bacteriological and Clinical Responses

**APPEARS THIS WAY
 ON ORIGINAL**

Pretreatment	Posttreatment				
	<i>H. pylori</i> negative (eradicated)	<i>H. pylori</i> positive (not eradicated)			
		Posttreatment susceptibility results ^b			
		S	I	R	No MIC
Susceptible ^b 44	41				3
Intermediate ^b 1	1				
Resistant ^b 11	7			2	2

^a56 Patients had pretreatment MIC values and eradication status at 6 weeks post-treatment

^bSusceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC 0.5 - 1.0 mcg/mL, Resistant (R) MIC ≥ 2 mcg/mL

Eradication of *H. pylori* occurred in 41 of the 44 patients with clarithromycin susceptible *H. pylori* isolates, in one patient with a clarithromycin intermediate MIC and in 7 of the 11 patients with clarithromycin resistant isolates. Posttreatment MICs were not available for 5 of the 7 patients who failed 14 day triple therapy. The other two patients that failed had clarithromycin resistant MICs pretreatment and posttreatment.

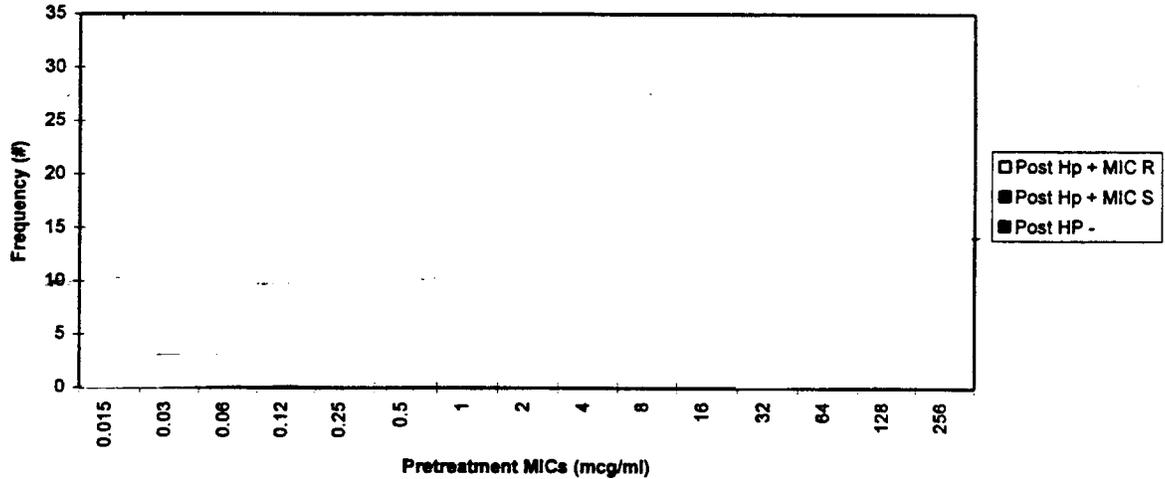
**APPEARS THIS WAY
 ON ORIGINAL**

Figure 7 is the presentation of the clarithromycin pretreatment agar dilution MIC results and clinical outcome for patients on the 10 day triple therapy regimen.

**APPEARS THIS WAY
 ON ORIGINAL**

Figure 7.

Clarithromycin Pretreatment Agar Dilution MIC Values and Bacteriological/Clinical Outcomes for Patients on 10 Day Triple Therapy



APPEARS THIS WAY
 ON ORIGINAL

The data corresponding to Figure 7 is presented in Table 8.

Table 8. Clarithromycin Agar Dilution Results for 46 Patients Treated with the 10 Day Triple Therapy Regimen^a

APPEARS THIS WAY
 ON ORIGINAL

Bacteriological and Clinical Responses

Pretreatment	Posttreatment				
	<i>H. pylori</i> negative (eradicated)	<i>H. pylori</i> positive (not eradicated)			
		Posttreatment susceptibility results ^b			
		S	I	R	No MIC
Susceptible ^b	42	40	1	1	
Intermediate ^b					
Resistant ^b	4	1		3	

^a46 Patients had pretreatment MIC values and eradication status at 6 weeks post-treatment

^bSusceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC 0.5 - 1.0 mcg/mL, Resistant (R) MIC ≥ 2 mcg/mL

Eradication of *H. pylori* occurred in 40 of the 42 patients with clarithromycin susceptible *H. pylori* isolates and in 1 of the 4 patients with clarithromycin resistant isolates. Emerging resistance occurred in one of the five patients who failed the 10 day triple therapy regimen. For this patient, the clarithromycin pretreatment MICs done by the agar dilution and Etest methodologies were 0.016 and > 256 respectively, while the posttreatment MICs by the agar dilution and Etest methodologies were 8 and > 256 respectively. Obviously, the correlation between the agar dilution and Etest values was poor for this patient.

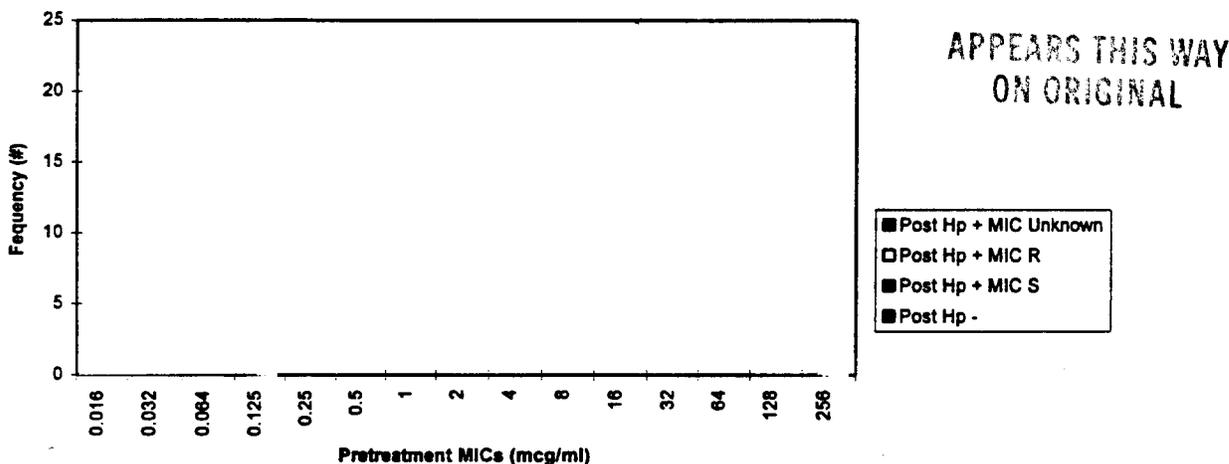
APPEARS THIS WAY
ON ORIGINAL

Figure 8 is the presentation of the clarithromycin pretreatment Etest MIC results and clinical outcome for patients on the 10 day triple therapy regimen.

APPEARS THIS WAY
ON ORIGINAL

Figure 8.

Clarithromycin Pretreatment Etest MIC Values and Bacteriological/Clinical Outcomes for Patients on 10 Day Triple Therapy



APPEARS THIS WAY
ON ORIGINAL

The data corresponding to Figure 8 is presented in Table 9.

APPEARS THIS WAY
ON ORIGINAL

Table 9. Clarithromycin Results for 58 Patients Treated with the 10 Day Triple Therapy Regimen^a

Bacteriological and Clinical Responses

Pretreatment	Posttreatment				
	<i>H. pylori</i> negative (eradicated)	<i>H. pylori</i> positive (not eradicated)			
		Posttreatment susceptibility results ^b			
		S	I	R	No MIC
Susceptible ^b 52	47	2			3
Intermediate ^b					
Resistant ^b 6	1			4	1

^a58 Patients had pretreatment MIC values and eradication status at 6 weeks post-treatment

^bSusceptible (S) MIC ≤ 0.25 mcg/mL, Intermediate (I) MIC 0.5 - 1.0 mcg/mL, Resistant (R) MIC ≥ 2 mcg/mL

Eradication of *H. pylori* occurred in 47 of the 52 patients with clarithromycin susceptible *H. pylori* isolates and in 1 of the 6 patients with clarithromycin resistant isolates. Posttreatment MICs were not available for 4 of the 10 patients who failed therapy.

**APPEARS THIS WAY
ON ORIGINAL**

CLARITHROMYCIN SUMMARY

Clarithromycin pretreatment resistance was 13.7% (17/124) by Etest and 11.3% (12/106) by agar dilution for all patients in the clinical studies to compare the 10 and 14 day triple therapy (lansoprazole, clarithromycin and amoxicillin) regimens. There was one documented case of emerging resistance for the *H. pylori* from a patient who failed the 10 day triple therapy regimen. Of the remaining patients who failed therapy, there were a couple with susceptible *H. pylori* isolates posttreatment and a number that did not have susceptibility test results.

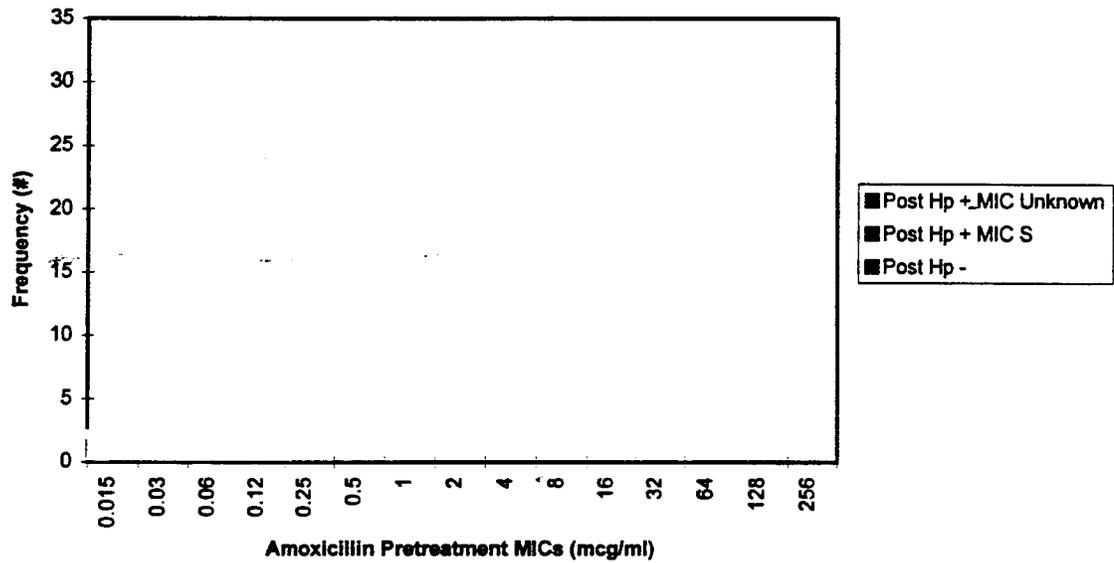
AMOXICILLIN SUSCEPTIBILITY TEST RESULTS AND CLINICAL/BACTERIOLOGICAL OUTCOMES

**APPEARS THIS WAY
ON ORIGINAL**

Figure 9 is the presentation of the amoxicillin pretreatment agar dilution MIC results and clinical outcome for patients on the 14 day triple therapy regimen.

Figure 9.

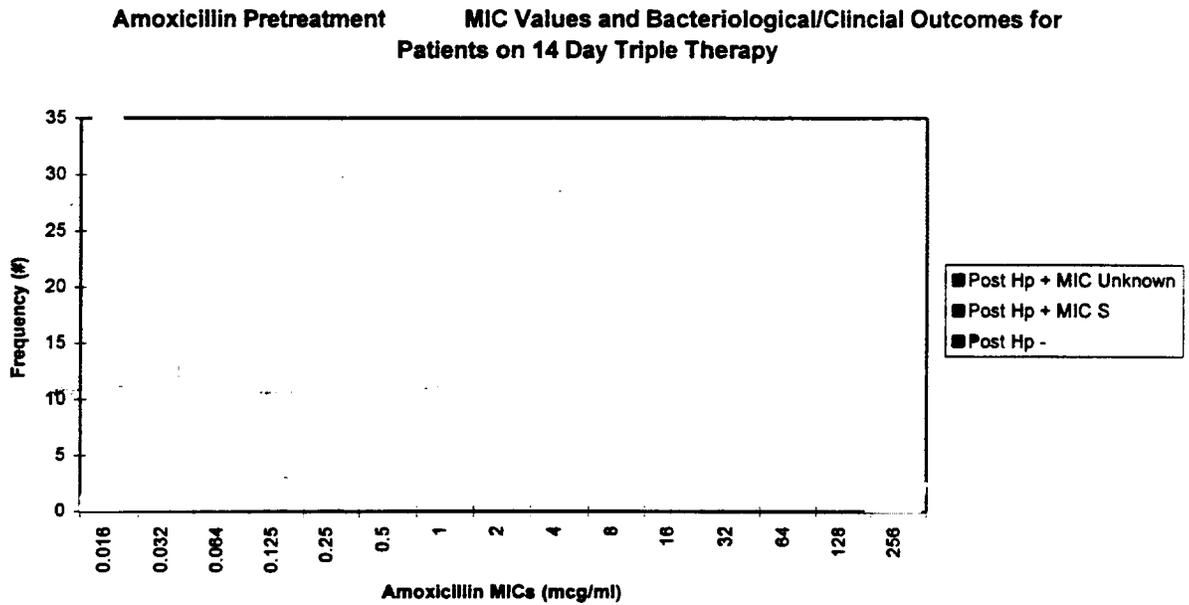
**Amoxicillin Pretreatment Agar Dilution MIC Values and
Bacteriological/Clinical Outcomes for Patients on 14 Day Triple Therapy**



The data corresponding to Figure 9 is presented in Table 10.

**APPEARS THIS WAY
ON ORIGINAL**

Figure 10.



APPEARS THIS WAY
ON ORIGINAL

The data corresponding to Figure 10 is presented in Table 11.

Table 11. Amoxicillin Etest Results for 56 Patients Treated with the 14 Day Triple Therapy Regimen^a

Bacteriological and Clinical Responses

APPEARS THIS WAY
ON ORIGINAL

Pretreatment	Posttreatment		
	<i>H. pylori</i> negative (eradicated)	<i>H. pylori</i> positive (not eradicated)	Posttreatment susceptibility results ^b
			S No MIC
Susceptible ^b	55	48	2 5
Undefined ^b	1	1	

^a56 Patients had pretreatment MIC values and eradication status at 6 weeks post-treatment

^bSusceptible (S) MIC ≤ 0.25 mcg/mL, undefined MIC > 0.25 mcg/mL

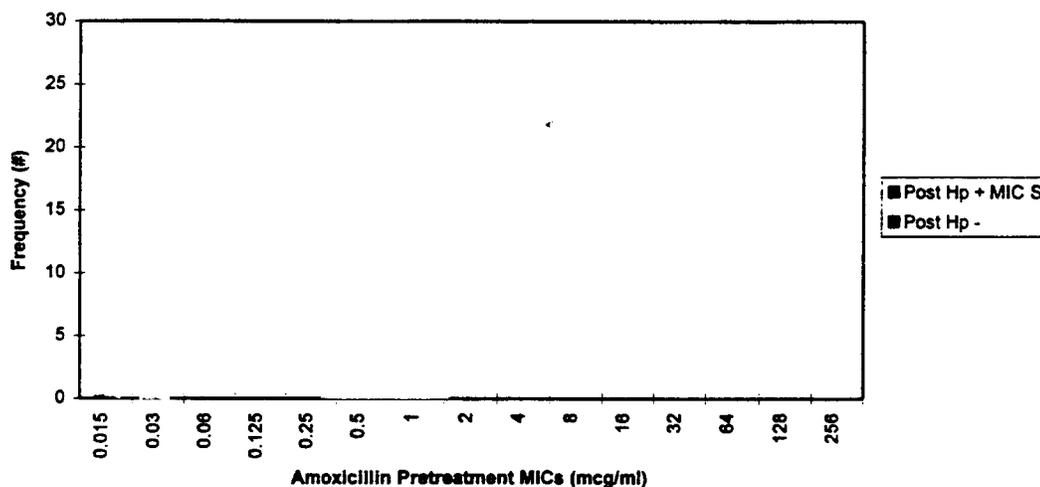
Eradication of *H. pylori* occurred in 48 of the 55 patients with amoxicillin susceptible *H. pylori* isolates and in one patient with an amoxicillin pretreatment MIC of ≥ 256 mcg/mL. Posttreatment MICs were not available for 5 of the 7 patients who failed therapy.

Figure 11 is the presentation of the amoxicillin pretreatment agar dilution MIC results and clinical outcome for patients on the 10 day triple therapy regimen.

Figure 11

APPEARS THIS WAY
ON ORIGINAL

Amoxicillin Pretreatment Agar Dilution MIC Values and
Bacteriological/Clinical Outcomes for Patients on 10 Day Triple Therapy



APPEARS THIS WAY
ON ORIGINAL

The data corresponding to Figure 11 is presented in Table 12.

APPEARS THIS WAY
ON ORIGINAL

Eradication of *H. pylori* occurred in 47 of the 57 patients with amoxicillin susceptible *H. pylori* isolates. Posttreatment MICs were not available for 4 of the 10 patients who failed therapy. One patient had an amoxicillin pretreatment MIC of 2.0 mcg/mL and the *H. pylori* was eradicated.

AMOXICILLIN SUMMARY

APPEARS THIS WAY
ON ORIGINAL

All amoxicillin pretreatment MICs were ≤ 0.25 mcg/mL except for the following: Two isolates had undefined amoxicillin pretreatment Etest MICs of >256 $\mu\text{g/mL}$ and 2 $\mu\text{g/mL}$ were not tested by agar dilution. In these two cases, the patients were eradicated of *H. pylori*. There were two isolates with undefined pretreatment amoxicillin MICs of 1.0 and 0.5 $\mu\text{g/mL}$ by agar dilution which had Etest values of 0.064 and 0.016 $\mu\text{g/mL}$ respectively. The patient with the agar dilution pretreatment MIC of 0.5 $\mu\text{g/mL}$ was eradicated of *H. pylori*. The patient with the pretreatment amoxicillin MIC of 1.0 $\mu\text{g/mL}$ failed therapy and had posttreatment amoxicillin MICs of 0.015 $\mu\text{g/mL}$ by agar dilution and 0.032 $\mu\text{g/mL}$ by Etest.

OVERALL POSTTREATMENT SUMMARY

APPEARS THIS WAY
ON ORIGINAL

There were minor differences in emerging clarithromycin resistance rates when comparing the 10 day and 14 day triple therapy regimens. In both treatment regimens the emerging clarithromycin resistance rates for the patients on clarithromycin, amoxicillin, and lansoprazole (10 or 14 day) were much lower than those seen with clarithromycin and lansoprazole (14 day). Increasing amoxicillin MICs posttreatment was not apparent.

The overall ability to obtain susceptibility testing results when the cultures were positive and the isolates were available was less than 50%. Additionally, the laboratory did not use the currently accepted testing methodology when doing agar dilution and the MICs were generally lower than the corresponding Etest results.

PATIENTS THAT FAILED 14 DAY TRIPLE THERAPY

APPEARS THIS WAY
ON ORIGINAL

For all evaluable patients (according to the Medical Officer) who failed 14 day triple therapy, the available pre and posttreatment amoxicillin and clarithromycin MIC results by agar dilution and Etest are presented in Table 14. If the susceptibility testing values are not available, ND (no data) is recorded.

Table 14. All Medical Officer Evaluable Patients that Failed on 14 Day Triple Therapy

Pre Amox	Pre Amox	Post Amox	Post Amox	Pre Clari	Pre Clari	Post Clari	Post Clari
Agar	Etest	Agar	Etest	Agar	Etest	Agar	Etest
0.015	0.016	0.015	0.016	32	256	128	256
0.015	0.023	ND	ND	0.12	0.064	ND	ND
0.015	0.016	ND	ND	0.015	0.016	ND	ND
0.015	0.016	ND	ND	0.015	0.016	ND	ND
0.03	0.016	ND	ND	32	256	ND	ND
0.06	0.064	ND	ND	4	256	ND	ND
0.12	0.094	0.12	0.064	8	256	4	256
ND	ND	0.015	0.032	ND	ND	0.03	256
ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	0.016	ND	ND	ND	256
ND	ND	ND	ND	ND	ND	ND	ND

ND=No Data

APPEARS THIS WAY
 ON ORIGINAL

BEST POSSIBLE COPY

According to the Medical Officer, there were 13 evaluable patients who failed the 14 day triple therapy regimen. Of these 13 patients, 6 patients had *H. pylori* isolates that were resistant to clarithromycin (2 were clarithromycin resistant pretreatment and posttreatment, 2 were clarithromycin resistant posttreatment with no pretreatment MICs, and 2 were clarithromycin resistant pretreatment with no posttreatment results). Three patients had amoxicillin and clarithromycin pretreatment susceptible MICs and no posttreatment values. Four patients had no amoxicillin or clarithromycin pretreatment or posttreatment values.

PATIENTS THAT FAILED 10 DAY TRIPLE THERAPY

APPEARS THIS WAY
 ON ORIGINAL

For all evaluable patients (according to the Medical Officer) who failed 10 day triple therapy, the available pre and posttreatment amoxicillin and clarithromycin MIC results by agar dilution and Etest are presented in Table 15. If the susceptibility testing values are not available, ND (no data) is recorded.

APPEARS THIS WAY
 ON ORIGINAL

Table 15. All Medical Officer Evaluable Patients that Failed on 10 Day Triple Therapy

Pre Amox Agar	Pre Amox Etest	Post Amox Agar	Post Amox Etest	Pre Clari Agar	Pre Clari Etest	Post Clari Agar	Post Clari Etest
0.015	ND	0.015	0.094	ND	ND	64	256
0.015	0.016	0.015	0.016	0.015	0.064	0.06	0.064
0.03	0.032	0.015	0.016	128	256	16	256
0.03	0.064	0.015	0.023	128	256	32	256
1	0.064	0.015	0.032	32	256	16	256
ND	0.016	0.015	0.023	ND	0.016	0.015	0.032
ND	0.016	0.03	0.016	0.015	256	8	256
ND	0.016	ND	ND	ND	0.016	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND
ND	0.023	ND	ND	ND	0.064	ND	ND
ND	0.064	ND	ND	ND	256	ND	ND
ND	ND	ND	0.016	ND	ND	ND	256
ND	ND	ND	0.016	ND	ND	8	256
ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND
ND	0.047	ND	ND	ND	0.016	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND
ND	ND	ND	ND	ND	ND	ND	ND

BEST POSSIBLE COPY

ND=No Data

**APPEARS THIS WAY
ON ORIGINAL**

According to the Medical Officer, there were 18 evaluable patients who failed the 10 day triple therapy regimen. Of these 18 patients, 8 patients had *H. pylori* isolates that were resistant to clarithromycin (4 were clarithromycin resistant pretreatment and posttreatment, 3 had no pretreatment MIC values but had clarithromycin resistant posttreatment MICs, and 1 was clarithromycin resistant pretreatment and with no posttreatment MICs). Three patients had amoxicillin and clarithromycin pretreatment susceptible MICs and no posttreatment values. Two patients had amoxicillin and clarithromycin susceptible pretreatment and posttreatment values. Five patients had no amoxicillin or clarithromycin pretreatment or posttreatment values.

**APPEARS THIS WAY
ON ORIGINAL**

CORRELATION OF AGAR DILUTION AND RESULTS

Clarithromycin Susceptibility Results

The correlation of MIC results determined by the E-test and the agar dilution methods for testing *H. pylori* isolates *in vitro* with clarithromycin is shown in Table 16.

Table 16.

Correlation of and Agar Dilution for Testing <i>H. pylori</i> Isolates <i>in vitro</i> with Clarithromycin (Number of isolates)								
E-test MIC (µg/mL)	Agar Dilution Log ₂ Differences							Total
	>-2 log ₂	-2 log ₂	-1 log ₂	0 log ₂	1 log ₂	2 log ₂	>2 log ₂	
0.016	0	0	0	38	5	5	1	49
0.03	0	0	19	1	0	1	0	21
0.06	0	21	2	3	1	0	0	27
0.125	17	0	3	2	0	0	0	22
0.25	2	0	1	0	0	0	0	3
0.5	1	0	0	0	0	0	0	1
32	1	0	0	0	0	0	0	1
256	20	1	5	2	0	0	0	28
Total	41	22	30	46	6	6	1	152
				30%				
				54%				
				72%				

In the comparison of and agar dilution for clarithromycin, 30% (46/152) of the isolates had identical MIC results; 54% (82/152) had MIC results within one log dilution; and 72% (110/152) had MIC results within two log dilutions.

Twenty-eight percent (28%; 42/152) of the isolates showed a greater than two-log-dilution difference between the two methods, usually with E-test greater than agar dilution. When the susceptibility breakpoints for clarithromycin (Susceptible ≤0.25 µg/mL, Intermediate 0.5 µg/mL to 1.0 µg/mL, and Resistant ≥2.0 µg/mL) were applied to the 42 isolates with a greater than two-log-dilution difference, 21 isolates were interpreted as susceptible and 17 were interpreted as resistant using either method. The remaining four isolates showed a discrepancy in interpretation between the two methods: all four isolates were resistant by E-test but susceptible by agar dilution.

**APPEARS THIS WAY
ON ORIGINAL**

Microbiology Reviewer Comments

Compared to other data received at the Agency and what is reported in the literature, it is unusual for the agar dilution results to be so much lower than the

results. Perhaps the difference is that _____ did not follow all of the methodological recommendations for agar dilution testing as established by the *H. pylori* Susceptibility Testing Study Group (a cooperative effort between the National Committee of Clinical Laboratory Standards (NCCLS), the FDA, academia, and industry).

**APPEARS THIS WAY
 ON ORIGINAL**

Amoxicillin Susceptibility Results

The correlation of MIC results determined by the E-test and the agar dilution method for testing *H. pylori* isolates *in vitro* with amoxicillin is shown in Table 17.

E-test MIC ($\mu\text{g/mL}$)	Agar Dilution Log ₂ Differences							Total
	>-2 log ₂	-2 log ₂	-1 log ₂	0 log ₂	.1 log ₂	2 log ₂	>2 log ₂	
0.016	0	0	0	78	23	0	1	102
0.03	0	0	11	1	1	0	0	13
0.06	0	9	7	0	1	0	0	17
0.125	1	1	1	3	0	0	1	7
Total	1	10	19	82	25	0	2	139
				59%				
			91%					
		98%						

In the comparison of E-test and agar dilution for amoxicillin, 59% (82/139) of the isolates had identical MIC results; 91% (126/139) had MIC results within one log dilution; and 98% (136/139) had MIC results within two log dilutions.

Two percent (2%; 3/139) of the isolates showed a greater than two-log-dilution difference between the two methods. When the susceptibility breakpoint for amoxicillin (Susceptible $\leq 0.25 \mu\text{g/mL}$) was applied to the three isolates with a greater than two-log-dilution difference all of the isolates were interpreted as susceptible for both methods. Those isolates with amoxicillin pretreatment Etest MIC of $>256 \mu\text{g/mL}$ and $2 \mu\text{g/mL}$ were not tested by agar dilution. In these two cases, the patients were eradicated of *H. pylori*. There were two isolates with pretreatment amoxicillin MICs of 1.0 and 0.5 $\mu\text{g/mL}$ by agar dilution which had Etest values of 0.064 and 0.016 $\mu\text{g/mL}$ respectively. The patient with the agar dilution pretreatment MIC of 0.5 $\mu\text{g/mL}$ was eradicated of *H. pylori*. The patient with the pretreatment amoxicillin MIC of 1.0 $\mu\text{g/mL}$ failed therapy and had

posttreatment amoxicillin MICs of 0.015 µg/mL by agar dilution and 0.032 µg/mL by

**APPEARS THIS WAY
ON ORIGINAL**

SUMMARY

There are some concerns regarding the microbiological aspects of this submission.

- 1) Obtaining positive culture results was less than 50% in patients where other diagnostic tests showed that *H. pylori* was present. The patients with positive cultures that had susceptibility test results was even less. Of the patients on the 10 day triple therapy regimen, 46 patients (38%) (46/120) had clarithromycin pretreatment susceptibility test results performed by the agar dilution methodology. Of the patients on the 14 day triple therapy regimen (M95-399), 48 patients (44%) (48/109) had clarithromycin pretreatment susceptibility test results performed by the agar dilution methodology. Of the patients on the 14 day triple therapy regimen (93-131, M95-392), 84 patients (67%) had clarithromycin pretreatment susceptibility test results performed by the Etest methodology. Of the patients on the 14 day dual therapy amoxicillin TID and lansoprazole TID regimen (93-131, M95-392), 70 patients (65%) (70/107) had clarithromycin pretreatment susceptibility test results performed by the Etest methodology.
- 2) While both the Etest and agar dilution methodologies were used in the study of the 10 day versus 14 day triple therapy regimens, the clarithromycin MICs obtained with the agar dilution methodology were generally lower (more susceptible) than those obtained by the Etest methodology. There were 27% (41/152) of the isolates that had agar dilution MICs $> -2 \log_2$ dilutions lower than the MICs obtained by Etest. This is contrary to what has been reported in other studies and in the literature. Additionally, some of the aspects of the agar dilution methodology as proposed by the *H. pylori* Susceptibility Testing Standardization Study Group were not followed. However using the data that are available which were obtained using the methodology of the sponsor, the following results were obtained.

Clarithromycin pretreatment resistance was 8.9% (74/836) by Etest in the 14 day dual and triple therapy clinical studies conducted in 1993 (M93-131, M95-392, M93-125, M93-130). Clarithromycin pretreatment resistance was 11.3% (12/106) by agar dilution and 13.7% (17/124) by Etest in the 10 and 14 day triple therapy (lansoprazole, clarithromycin and amoxicillin) clinical study conducted in 1995 (M95-399). Although it appears that clarithromycin pretreatment resistance is increasing, the total number of patients tested in the later study is lower. One patient on the 14 day triple therapy regimen had an unconfirmed pretreatment amoxicillin minimum inhibitory concentration (MIC) was ≥ 256 µg/mL by Etest and the patient was eradicated of *H. pylori*.

Clarithromycin susceptibility results and their correlation with clinical and bacteriological outcomes are shown in Table 18.

APPEARS THIS WAY
 ON ORIGINAL

Table 18.

Clarithromycin Susceptibility Test Results and Clinical/Bacteriological Outcomes^a

Clarithromycin Pretreatment Results	Clarithromycin Posttreatment Results				
	<i>H. pylori</i> negative - eradicated	<i>H. pylori</i> positive - not eradicated			
		Posttreatment susceptibility results			
		S ^b	I ^b	R ^b	No MIC
Triple Therapy 14 Day (lansoprazole/amoxicillin/clarithromycin) (M95-399, M93-131, M95-392)					
Susceptible ^b	112	105			7
Intermediate ^b	3	3			
Resistant ^b	17	6		7	4
Triple Therapy 10 Day (lansoprazole/amoxicillin/clarithromycin) (M95-399)					
Susceptible ^b	42	40	1	1	
Intermediate ^b					
Resistant ^b	4	1		3	

^a Includes only patients with pretreatment clarithromycin susceptibility test results

^b Susceptible (S) MIC ≤ 0.25 µg/mL, Intermediate (I) MIC 0.5 - 1.0 µg/mL, Resistant (R) MIC ≥ 2 µg/mL

APPEARS THIS WAY
 ON ORIGINAL

Amoxicillin susceptibility results and their correlation with clinical and bacteriological outcomes are shown in Table 19.

Table 19.

Amoxicillin Susceptibility Test Results and Clinical/Bacteriological Outcomes^a

APPEARS THIS WAY
 ON ORIGINAL

Amoxicillin Pretreatment Results	Amoxicillin Posttreatment Results				
	<i>H. pylori</i> negative eradicated	<i>H. pylori</i> positive - not eradicated (# failures with clarithromycin resistance)			
		Posttreatment susceptibility results			
		S ^b	Undefined ^b	No MIC	
Dual Therapy 14 Day (lansoprazole/amoxicillin)^c (M93-131, M95-392)					
Susceptible ^b	69	49	11 (0)	1 (0)	8 (3)
Undefined ^b	1	0	1 (0)		
Triple Therapy 14 Day (lansoprazole/amoxicillin/clarithromycin) (M95-399, M93-131, M95-392)					
Susceptible ^b	127	110	6 (5)		11 (4)
Undefined ^b	3	2	1		
Triple Therapy 10 Day (lansoprazole/amoxicillin/clarithromycin)^c (M93-399)					
Susceptible ^b	40	36	4 (3)		
Undefined ^b	2	1	1 (1)		

^a Includes only patients with pretreatment amoxicillin susceptibility test results

^b Susceptible (S) MIC ≤ 0.25 µg/mL, Undefined > 0.25 µg/mL

^c Clarithromycin susceptibility results should not be factor when the patient is treated with lansoprazole and amoxicillin

APPEARS THIS WAY
 ON ORIGINAL

The data in Table 19 indicate that many of the patients who fail triple therapy are clarithromycin resistant. The amoxicillin MIC values appear to play a lesser role than clarithromycin MIC values when evaluating clinical outcome.

Posttreatment results indicate that there were fewer failures on the triple therapy regimens compared to the dual therapy (lansoprazole and clarithromycin or lansoprazole and amoxicillin) regimens. While there are a number of clarithromycin posttreatment MIC values that are missing, it appears that there is less emergence of clarithromycin resistance on triple therapy compared to dual therapy (clarithromycin and a proton pump inhibitor). On the 10 day triple

therapy regimen, there was one patient with emerging clarithromycin resistance. On the 14 day triple therapy regimen, there were seven patients who failed therapy who did not have susceptibility results.

There were no major differences in emerging clarithromycin resistance rates when comparing the 10 day and 14 day triple therapy regimens. In both treatment regimens the emerging clarithromycin resistance rates for the patients on clarithromycin, amoxicillin, and lansoprazole (10 or 14 day) were much lower than those seen with clarithromycin and lansoprazole (14 day). Increasing amoxicillin MICs posttreatment was not apparent. Shortening the course of therapy does not significantly impact the development of antimicrobial resistance.

**APPEARS THIS WAY
ON ORIGINAL**

NDA REVIEW REFERENCES:

1. **Iwahi T, Satoh H, Nakao M, et al.** Lansoprazole, a novel benzimidazole proton pump inhibitor, and its related compounds have selective activity against *Helicobacter pylori*. *Antimicrobial Agents and Chemotherapy*. 1991;35:490-6.
2. **Nagata K, Satoh H, Iwahi T, Shimoyama T, Tamura T.** Potent inhibitory action of the gastric proton pump inhibitor lansoprazole against urease activity of *Helicobacter pylori*: unique action selective for *H. pylori* cells. *Antimicrobial Agents and Chemotherapy*. 1993;37:769-74.
3. **Hardy DJ, Hanson CW, Hensey DM, Beyer JM, Fernandes PB.** Susceptibility of *Campylobacter pylori* to macrolides and fluoroquinolones. *Journal of Antimicrobial Chemotherapy*. 1988;22:631-6.
4. **Malanoski GJ, Eliopoulos GM, Ferraro MJ, Moellering RC Jr.** Effect of pH variation on the susceptibility of *Helicobacter pylori* to three macrolide antimicrobial agents and temafloxacin. *European Journal of Clinical Microbiology and Infectious Diseases*. 1993;12:131-3.
5. **Schalen C, Cederbrant G, Kahlmeter G, Kamme C.** *In vitro* effect of clarithromycin combined with 14-OH-clarithromycin, erythromycin, amoxicillin, metronidazole, or omeprazole against *Helicobacter pylori*. *Gastroenterology*. 1994;106:A174.
6. **Graham DY.** Determinants of antimicrobial effectiveness in *H. pylori* gastritis. In: *Helicobacter pylori: basic mechanisms to clinical cure*. Hunt RH, Tytgat GNJ, eds. Dordrecht, The Netherlands: Kluwer Academic Publishers; 1994:531-7.
7. **Hunt RH.** Hp and pH: implications for the eradication of *Helicobacter pylori*. *Scand J Gastroenterology*. 1993;196:12-6.

8. **Flamm RK, Beyer J, Tanaka SK, Clement J.** Kill kinetics of five antibiotics against *Helicobacter pylori*. 33rd Interscience Conference on Antimicrobial Agents and Chemotherapy; 1993. Abstract #232.
9. **Flamm RK, Beyer J, Tanaka SK, Clement J.** Kill kinetics and activity of antibiotics against *Helicobacter pylori*. 2nd International Conference of Macrolides, Azalides, and Streptogramins; 1994. Abstract #139.
10. **Versalovic J, Shortridge D, Kibler K, et al.** Mutations in 23S rRNA are associated with clarithromycin resistance of *Helicobacter pylori*. *Antimicrobial Agents and Chemotherapy*. 1996;40:477-80.
11. **Millar MR, Pike J.** Bactericidal activity of antimicrobial agents against slowly growing *Helicobacter pylori*. *Antimicrobial Agents and Chemotherapy*. 1992;36:185-7.
12. **Goldman RC, Zakula D, Flamm R, Beyer J, Capobianco J.** Tight binding of clarithromycin, its 14(R)-hydroxy metabolite, and erythromycin to *Helicobacter pylori* ribosomes. *Antimicrobial Agents and Chemotherapy*. 1994;38:1496-500.
13. **Dixon JS.** *Helicobacter pylori* eradication: unravelling the facts. *Scand J Gastroenterol*. 1995;30 Suppl 212:48-62.
14. **Burette A, Glupczynski Y, DePerez C, et al.** Omeprazole alone or in combination with clarithromycin for eradication of *H. pylori*: results of a randomized, double-blind controlled study. *Gastroenterology*. 1993;104:A49.
15. **Peterson WL, Graham D, Marshall B, et al.** Clarithromycin as monotherapy for eradication of *Helicobacter pylori*: a randomized, double-blind trial. *American Journal of Gastroenterology*. 1993;88:1860-4.
16. **Soll, AH.** Pathogenesis of peptic ulcer and implications for therapy. Seminars in Medicine of the Beth Israel Hospital, Boston. *New England Journal of Medicine*. 1990;322:909-16.
17. **Droy-Lefaix MT, Bonneville F, Moyen EN, Geraud G, Combrier E, Fauchere JL.** *Campylobacter pylori* and gastritis: a new animal model in germ-free rats. *Gastroenterology*. 1989;96:A130.
18. **Fox JG, Otto G, Murphy JC, Taylor NS, Lee A.** Gastric colonization of the ferret with *Helicobacter* species: natural and experimental infections. *Reviews of Infectious Disease*. 1991;13(S8):S671-S680.

APPEARS THIS WAY
ON ORIGINAL

4 Page(s) Redacted

DRAFT LABELING

CONCLUSIONS:

This application has approval from the microbiological perspective provided the package insert is accepted by the sponsor.

APPEARS THIS WAY
ON ORIGINAL

/S/

Linda J. Utrup, Ph.D.

CONCURRENCES:

HFD-590/Dep Div Dir _____

/S/

Signature

12/19/98
revisions
2/12/98

Date

CC:

- HFD-590/Original NDA #20-406
- HFD-590/Division File
- HFD-590/DivDir/Goldberger
- HFD-520/MO/Girardi
- HFD-590/CSO/Anderson
- HFD-180/CSO/Walsh
- HFD-180/MO/Senior
- HFD-590/Micro/Utrup

APPEARS THIS WAY
ON ORIGINAL